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SPECIFICATION

SUBSTITUTED PHENETHYLAMINE DERIVATIVES

5 TECHNICAL FIELD

This invention relates to substituted phenethylamine derivatives that function as a motilin receptor antagonist and that are useful as medicines.

10 BACKGROUND ART

Motilin, which is one of the gastrointestinal hormones, is a straight-chained peptide consisting of 22 amino acids and is well known to be responsible for regulating the motility of the gastrointestinal tract in animals including human. It has been reported that exogenously administered motilin causes contractions in humans and dogs that are similar to interdigestive migrating contractions, thus promoting gastric emptying (Itoh et al., Scand. J. Gastroenterol., 11, 93-110 (1976); Peeters et al., Gastroenterology 102, 97-101 (1992)). Hence, erythromycin derivatives which are an agonist of motilin are under development as an gastrointestinal tract motor activity enhancer (Satoh et al., J. Pharmacol. Exp. Therap., 271, 574-579 (1994); Lartey et al., J. Med. Chem., 38, 1793-1798 (1995); Drug of the Future, 19, 910-912 (1994)).

Peptide and polypeptide derivatives have been reported as antagonists of motilin receptors (Depoortere et

al., Eur. J. Pharmacol., 286, 241-247 (1995); Poitras et al., Biochem. Biophys. Res. Commun., 205, 449-454 (1994); Takanashi et al., J. Pharmacol. Exp. Ther., 273, 624-628 (1995)). These derivatives are used as a pharmacological
5 tool in the study of the action of motilin on the motility of the gastrointestinal tract and in the research and development of medicines in the field of the art contemplated by the invention.

Motilin receptors had been known to occur principally
10 in the duodenum but recently it has been shown that they also occur in the large intestine, or the lower part of the gastrointestinal tract (William et al., Am. J. Physiol., 262, G50-G55 (1992)), and this indicates the possibility that motilin is involved not only in the motility of the
15 upper part of the gastrointestinal tract but also in the motility of its lower part.

Reports have also been made of the cases of hypermotilinemia in patients with irritable bowel syndrome who were manifesting diarrhea and in patients with
20 irritable bowel syndrome who were under stress (Preston et al., Gut, 26, 1059-1064 (1985); Fukudo et al., Tohoku J. Exp. Med., 151, 373-385 (1987)) and this suggests the possibility that increased blood motilin levels are involved in the disease. Other diseases that have been
25 reported to involve hypermotilinemia include crohn's disease, ulcerative colitis, pancreatitis, diabetes mellitus, obesity, malabsorption syndrome, bacterial diarrhea, atrophic gastritis and postgastroenterectomy

an optionally substituted heterocyclic ring, C₃₋₇cycloalkyl or phenyl;

R₁, R₂, R₃, R₄ and R₅ are hydrogen, halogen, hydroxy, amino, trifluoromethyl or nitrile and at least one of R₁, R₂,

5 R₃, R₄ and R₅ is halogen, trifluoromethyl or nitrile;

R₆ is hydrogen, optionally substituted straight-chained or branched C₁₋₃alkyl, amino or hydroxy;

R₇ is hydrogen, optionally substituted straight-chained or branched C₁₋₃alkyl, optionally substituted amino
10 or hydroxy;

R₈ is hydrogen, methyl or ethyl;

R₉ is optionally substituted straight-chained or branched C₁₋₆alkyl, optionally substituted straight-chained or branched C₂₋₆alkenyl, optionally substituted straight-
15 chained or branched C₂₋₆alkynyl, C₃₋₇cycloalkyl or optionally substituted phenyl;

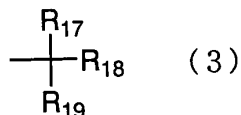
R₂₀ is hydrogen or straight-chained or branched C₁₋₃alkyl or R₉ and R₂₀ may together form C₃₋₇cycloalkyl;

R₁₀ is hydrogen or straight-chained or branched
20 C₁₋₃alkyl;

R₁₁ is hydrogen, optionally substituted straight-chained or branched C₁₋₃alkyl, -CO-N(R₁₄)R₁₅, carboxyl or an optionally substituted heterocyclic ring;

R₁₂ is hydroxy or -OR₁₆;

25 R₁₃ is hydrogen, straight-chained or branched C₁₋₆alkyl, straight-chained or branched C₂₋₆alkenyl, straight-chained or branched C₂₋₆alkynyl or a group of Formula (3):



5 R_{14} and R_{15} , which may be the same or different, are hydrogen, optionally substituted straight-chained or branched C_{1-4} alkyl, C_{3-7} cycloalkyl, straight-chained or branched C_{1-4} alkyloxy, straight-chained or branched C_{1-4} alkylsulfonyl or a heterocyclic ring, or R_{14} and R_{15} , as - $N(R_{14})R_{15}$, form optionally substituted 3- to 7-membered cyclic amine;

R_{16} is straight-chained C_{1-4} alkyl;

10 R_{17} is hydrogen or methyl;

R_{18} and R_{19} , together form cycloalkyl or C_{3-7} cycloalkenyl;

X is carbonyl or methylene;

Y is carbonyl or methylene;

15 provided that

when Cy is 3-indolyl,

(i) R_{11} is an optionally substituted heterocyclic ring; or

(ii) R_6 is hydrogen, R_7 is amino, R_8 is methyl, R_9 is isopropyl, R_{20} is hydrogen, R_{10} is methyl, R_{11} is carbamoyl, R_{12} is hydroxy, R_{13} is tert-butyl, X is carbonyl and Y is carbonyl, and

when Cy is cyclohexyl or phenyl, R_{11} is an optionally substituted heterocyclic ring,

25 or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides a medicine

containing a compound of Formula (1) as an active ingredient. Further, the present invention provides a motilin receptor antagonist composition containing the compound. The present invention also provides a
 5 gastrointestinal motility suppressor agent containing the compound as an active ingredient. Further, the present invention provides a therapeutic of hypermotilinemia containing the compound as an active ingredient.

The present invention also provides compounds of
 10 Formula (4):



wherein

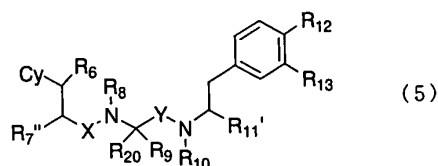
Cy, R₆, R₈, R₉, R₂₀, R₁₀, R₁₂, R₁₃, X and Y are as defined in claim 1;

15 R₇' is hydrogen, straight-chained or branched C₁₋₃alkyl optionally having at least one protected substituent, amino optionally having at least one protected substituent or protected hydroxy;

R₁₁" is hydrogen, optionally substituted straight-
 20 chained or branched C₁₋₃alkyl, -CO-N(R₁₄)R₁₅, wherein R₁₄ and R₁₅ are as defined in claim 1, carboxyl, straight-chained or branched C₁₋₃alkyl having protected amino or an optionally substituted heterocyclic ring;
 or hydrates or pharmaceutically acceptable salts thereof.

25 The present invention also provides compounds of

Formula (5):



wherein:

Cy, R₆, R₈, R₉, R₂₀, R₁₀, R₁₂, R₁₃, X and Y are as defined

5 in claim 1;

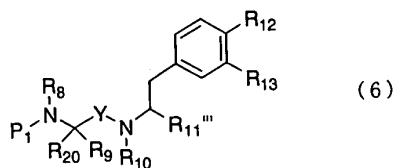
R₇ is hydrogen, straight-chained or branched C₁₋₃alkyl optionally having at least one optionally protected substituent, amino optionally having at least one optionally protected substituent or optionally protected

10 hydroxy;

R₁₁' is hydrogen, straight-chained or branched C₁₋₃alkyl optionally having at least one protected substituent, -CO-N(R₁₄)R₁₅ wherein R₁₄ and R₁₅ are as defined in claim 1, carboxyl or an optionally substituted heterocyclic ring;

15 or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of Formula (6):



20 wherein:

R₈, R₉, R₂₀, R₁₀, R₁₂, R₁₃ and Y are as defined in claim

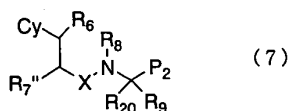
1;

P₁ is hydrogen or a protecting group of amine;

R₁₁''' is hydrogen, optionally substituted straight-

chained or branched C₁₋₃alkyl, -CO-N(R₁₄)R₁₅ wherein R₁₄ and R₁₅
 are as defined in claim 1, carboxyl, straight-chained or
 branched C₁₋₃alkyl having protected amino or an optionally
 substituted heterocyclic ring;
 5 or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of
 Formula (7):



wherein:

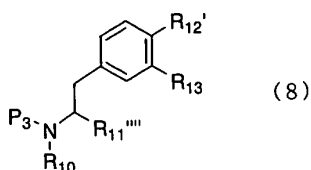
Cy, R₆, R₈, R₉, R₂₀ and X are as defined in claim 1;

R₇ is hydrogen, straight-chained or branched C₁₋₃alkyl
 optionally having at least one optionally protected
 15 substituent, amino optionally having at least one
 optionally protected substituent or optionally protected
 hydroxy;

P₂ is optionally protected carboxyl, formyl or methyl
 having a leaving group;

20 or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of
 Formula (8)



wherein:

R_{10} and R_{13} are as defined in claim 1;

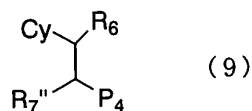
P_3 is hydrogen or a protecting group of amine;

R_{11} is hydrogen, optionally substituted straight-
5 chained or branched C_{1-3} alkyl, $-CO-N(R_{14})R_{15}$ wherein R_{14} and R_{15}
are as defined in claim 1, carboxyl, straight-chained or
branched C_{1-3} alkyl having protected amino or an optionally
substituted heterocyclic ring;

R_{12} is hydroxy or $-OR_{16}$ wherein R_{16} is as defined in
10 claim 1;
or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of
Formula (9)

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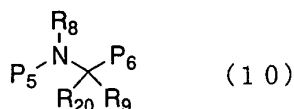
wherein:

Cy and R_6 are as defined in claim 1;

R_7 is hydrogen, straight-chained or branched C_{1-3} alkyl
20 optionally having at least one optionally protected
substituent, amino optionally having at least one
optionally protected substituent or optionally protected
hydroxy;

P_4 is optionally protected carboxyl, formyl or methyl
25 having a leaving group;
or hydrates or pharmaceutically acceptable salts thereof.

The present invention also provides compounds of
Formula (10)



5 wherein:

R_8 , R_9 and R_{20} are as defined in claim 1;

P_5 is hydrogen or a protecting group of amine;

P_6 is optionally protected carboxyl, formyl or methyl
having a leaving group;

10 or hydrates or pharmaceutically acceptable salts thereof.

In the definition of the compounds of Formula (1),
halogen as R_1 , R_2 , R_3 , R_4 and R_5 of Formula (2) as Cy is
preferably fluorine or chlorine, with fluorine being more
preferred. When at least 2 of R_1 to R_5 are halogen, they
15 may be the same or different halogen, however it is
preferable that they are the same. The number of halogen
atoms is preferably 1 to 3 and more preferably 1 or 2.

Preferably, at least one of R_1 , R_2 , R_3 , R_4 and R_5 of
Formula (2) as Cy is halogen, trifluoromethyl or nitrile
20 and the others are independently hydrogen or hydroxy.

Preferably, R_3 is halogen, trifluoromethyl or nitrile or R_2
and R_3 are the same kind of halogen. Preferred compounds
include those in which R_3 is halogen and R_1 , R_2 , R_4 and R_5
are hydrogen; those in which R_2 and R_3 are the same halogen
25 and R_1 , R_4 and R_5 are hydrogen; and those in which at least
one of R_1 , R_2 , R_3 , R_4 and R_5 is trifluoromethyl or nitrile
and the others are hydrogen, halogen or hydroxy.

Preferred examples of the group of Formula (2) as Cy include 4-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 2-fluoro-4-hydroxyphenyl, 3-fluoro-4-hydroxyphenyl, 4-trifluoromethylphenyl and 4-cyanophenyl, more preferably 4-fluorophenyl and 4-chlorophenyl, with 4-fluorophenyl being most preferred.

Preferred examples of the heterocyclic ring of the optionally substituted heterocyclic ring as Cy include aliphatic or aromatic 5- to 7-membered mono- or fused-rings containing at least one hetero atom selected from among N, S and O; specific examples include pyridyl, pyrazinyl, furyl, thienyl, pyrrolyl, imidazolyl, indolyl, quinolinyl, benzoimidazolyl, benzodiazepinyl, benzofuryl, pyrrolidinyl, piperazinyl, piperidinyl and tetrahydroisoquinolinyl, with indolyl being preferred.

Exemplary substituents of the optionally substituted heterocyclic ring as Cy include hydroxy, methoxy, amino, methyl, ethyl, trifluoromethyl, carboxy, methoxycarbonyl and oxo. The heterocyclic ring may have one or more of the above-mentioned substituents, which may be the same or different.

Preferably, the optionally substituted heterocyclic ring of Cy is 3-indolyl.

25 Preferably, the C₃₋₇cycloalkyl as Cy is cyclopentyl or
cyclohexyl.

While Cy has the definitions set forth above, Cy is preferably Formula (2) or an optionally substituted

heterocyclic ring, more preferably 4-fluorophenyl, 3-fluorophenyl, 3,4-difluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 2-fluoro-4-hydroxyphenyl, 3-fluoro-4-hydroxyphenyl, 4-trifluoromethylphenyl, 4-cyanophenyl and 3-indolyl, with 4-fluorophenyl being particularly preferred.

The alkyl of the optionally substituted straight-chained or branched C₁₋₃alkyl as R₆ is preferably methyl or ethyl.

10 Exemplary substituents of the optionally substituted straight-chained or branched C₁₋₃alkyl as R₆ include halogen, with fluorine being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

15 The optionally substituted straight-chained or branched C₁₋₃alkyl as R₆ is preferably methyl, ethyl, fluoromethyl or trifluoromethyl, with methyl being particularly preferred.

While R₆ has the definitions set forth above, R₆ is preferably hydrogen or methyl.

The alkyl of the optionally substituted straight-chained or branched C₁₋₃alkyl as R₇ is preferably methyl.

Exemplary substituents of the optionally substituted straight-chained or branched C₁₋₃alkyl as R₇ include halogen, hydroxy and amino, with hydroxy being preferred. The alkyl may have one or more of the above-mentioned substituents, which may be the same or different.

The optionally substituted straight-chained or

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branched C₁₋₃alkyl as R₇ is preferably methyl or trifluoromethyl, with methyl being particularly preferred.

Exemplary substituents of the optionally substituted amino as R₇ include straight-chained or branched C₁₋₃alkyl, with methyl and ethyl being preferred. The amino may have one or more of the above-mentioned substituents, which may be the same or different.

The optionally substituted amino as R₇ is preferably amino optionally substituted with one or more of the same or different kinds of straight-chained or branched C₁₋₃alkyl; specific examples include amino, methylamino, dimethylamino and ethylamino, with amino and methylamino being particularly preferred.

While R₇ has the definitions set forth above, R₇ is preferably hydrogen or optionally substituted amino, with hydrogen, amino and methylamino being particularly preferred.

R₈ is preferably hydrogen or methyl.

The alkyl of the optionally substituted straight-chained or branched C₁₋₆alkyl as R₉ is preferably straight-chained or branched C₁₋₅alkyl, e.g., methyl, ethyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl and neopentyl.

Exemplary substituents of the optionally substituted straight-chained or branched C₁₋₆alkyl as R₉ include substituted or unsubstituted phenyl (e.g., phenyl, tolyl, para-hydroxyphenyl and para-fluorophenyl), C₃₋₇cycloalkyl, heterocyclic rings (e.g., pyrazyl, furyl, thienyl, pyrrolyl,

imidazolyl and quinolinyl) and halogen, with phenyl, cyclohexyl and thienyl being preferred.

The optionally substituted straight-chained or branched C₁₋₆alkyl as R₉ is preferably methyl, isopropyl, 5 isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, para-fluorobenzyl, 2-thienylmethyl, 3-indolylmethyl, benzyl, para-hydroxybenzyl, phenethyl or cyclohexylmethyl.

The alkenyl of the optionally substituted straight-chained or branched C₂₋₆alkenyl as R₉ is preferably vinyl, 2- 10 propenyl, 2-propen-1-yl, 2-buten-1-yl or 2-isobuten-1-yl, with 2-propen-1-yl being more preferred.

Exemplary substituents of the optionally substituted straight-chained or branched C₂₋₆alkenyl as R₉ include phenyl, tolyl, para-hydroxyphenyl and para-fluorophenyl.

15 The optionally substituted straight-chained or branched C₂₋₆alkenyl as R₉ is preferably 2-propen-1-yl.

The alkynyl of the optionally substituted straight-chained or branched C₂₋₆alkynyl as R₉ is preferably ethynyl, propargyl or 2-butyn-1-yl, with 2-butyn-1-yl being 20 preferred.

Exemplary substituents of the optionally substituted straight-chained or branched C₂₋₆alkynyl as R₉ include halogen, phenyl, tolyl, para-hydroxyphenyl and para-fluorophenyl.

25 The optionally substituted straight-chained or branched C₂₋₆alkynyl as R₉ is preferably 2-butyn-1-yl.

The C₃₋₇cycloalkyl as R₉ is preferably cyclopentyl or cyclohexyl.

Exemplary substituents of the optionally substituted phenyl as R_9 include hydroxy, amino, methyl, ethyl and halogen. The phenyl may have one or more of the above-mentioned substituents, which may be the same or different.

5 The optionally substituted phenyl as R_9 is preferably phenyl.

The C_{3-7} cycloalkyl formed by R_9 and R_{20} is preferably cyclopentyl or cyclohexyl.

10 While R_9 has the definitions set forth above, R_9 is preferably isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, cyclohexyl, 2-thienylmethyl, 3-indolylmethyl, phenyl, benzyl, para-hydroxybenzyl, para-fluorobenzyl or cyclohexylmethyl, with isopropyl being particularly preferred.

15 The straight-chained or branched C_{1-3} alkyl as R_{20} is preferably methyl.

R_{20} is preferably hydrogen.

R_{10} is preferably hydrogen or methyl.

20 The alkyl of the optionally substituted straight-chained or branched C_{1-3} alkyl as R_{11} is preferably methyl.

Exemplary substituents of the optionally substituted straight-chained or branched C_{1-3} alkyl as R_{11} include amino optionally substituted with one or more of the same or different kind of straight-chained or branched C_{1-3} alkyl (e.g., amino, methylamino, dimethylamino and ethylamino), 25 optionally substituted 3- to 7-membered cyclic amino (exemplary substituents of the cyclic amino include hydroxy, amino, carboxyl, carbamoyl and methyl), hydroxy, methoxy,

chained or branched C_{1-4} alkyl as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} include methyl, ethyl, propyl, isopropyl, tert-butyl, hydroxymethyl, methoxymethyl, 2-hydroxyethyl, 2-aminoethyl, 2-hydroxy-2-methylpropyl, 2-hydroxy-2-methylpropyl, 2-amino-2-methylpropyl and methanesulfonylmethyl, with methyl, ethyl, propyl, isopropyl, tert-butyl, hydroxymethyl, methoxymethyl and methanesulfonylmethyl being preferred.

The C_{3-7} cycloalkyl as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} is preferably cyclopropyl.

10 The straight-chained or branched C_{1-4} alkyloxy as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} is preferably methoxy.

The straight-chained or branched C_{1-4} alkylsulfonyl as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} is preferably methanesulfonyl.

15 Examples of the heterocyclic ring as R_{14} and R_{15} in $-CO-N(R_{14})R_{15}$ as R_{11} include aliphatic or aromatic 5- or 6-membered rings containing at least one hetero atom selected from among N, S and O; specific examples include 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazinyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl and triazolyl, with 2-pyridyl being preferred.

20 The 3- to 7-membered cyclic amine of the optionally substituted 3- to 7-membered cyclic amine as $-N(R_{14})R_{15}$ as R_{11} include aziridine, azetidine, pyrrolidine, piperidine, piperazine and morpholine, with piperazine and morpholine being preferred. Exemplary substituents of the optionally substituted 3- to 7-membered cyclic amine include hydroxy, amino, carboxyl, alkoxycarbonyl, carbamoyl, methyl,

carboxymethyl, alkoxy carbonylmethyl and methylsulfonyl.

The optionally substituted 3- to 7-membered cyclic amine as $-N(R_{14})R_{15}$ or $-CO-N(R_{14})R_{15}$ as R_{11} is preferably 4-carboxymethylpiperazine, 4-ethoxycarbonylpiperazine, 4-methylsulfonylpiperazine or morpholine.

The $-CO-N(R_{14})R_{15}$ as R_{11} is preferably carbamoyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tert-butylcarbamoyl, 2-pyridylcarbamoyl, methanesulfonylmethylcarbamoyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl, methoxymethylcarbamoyl, methoxycarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl and 4-methylsulfonyl-1-piperazinecarbonyl, with carbamoyl and ethylcarbamoyl being more preferred.

Examples of the heterocyclic ring of the optionally substituted heterocyclic ring as R_{11} include aliphatic or aromatic 5- or 6-membered rings containing at least one hetero atom selected from among N, S and O. Exemplary substituents of the heterocyclic ring include oxo, hydroxy, methyl, ethyl and trifluoromethyl; the heterocyclic ring may have one or more of the above-mentioned substituents, which may be the same or different. Specific examples of the optionally substituted heterocyclic ring include furyl, thienyl, pyrrolyl, oxazolyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-thiadiazol-2-yl, 1,3,4-triazol-2-yl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 4-pyrimidinon-2-yl, 6-methyl-4-pyrimidinon-2-yl

and imidazolidine-2,4-dione-5-yl, with 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl and 6-methyl-4-pyrimidino-2-yl being preferred.

While R_{11} has the definitions set forth above, R_{11} is preferably methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tert-butylcarbamoyl, 2-pyridylcarbamoyl, methanesulfonylmethylcarbamoyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl, methoxymethylcarbamoyl, methoxycarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl, 4-methylsulfonyl-1-piperazinecarbonyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl and 6-methyl-4-pyrimidinon-2-yl, with carbamoyl and ethylcarbamoyl being more preferred.

The straight-chained C_{1-4} alkyl as R_{16} of $-OR_{16}$ as R_{12} is preferably methyl.

R_{12} is preferably hydroxy.

The straight-chained or branched C_{1-6} alkyl as R_{13} is preferably straight-chained or branched C_{2-5} alkyl, more preferably branched C_{3-5} alkyl, and most preferably tert-butyl.

The straight-chained or branched C_{2-6} alkenyl as R_{13} is preferably straight-chained or branched C_{3-5} alkenyl and more preferably branched C_{3-5} alkenyl.

The straight-chained or branched C_{2-6} alkynyl as R_{13} is

preferably straight-chained or branched C₃₋₅alkynyl and more preferably branched C₃₋₅alkynyl.

R₁₇ in Formula (3) as R₁₃ is preferably methyl.

The C₃₋₇cycloalkyl formed by R₁₈ and R₁₉ in Formula (3)
5 as R₁₃ is preferably C₃₋₅cycloalkyl.

The C₃₋₇ cycloalkenyl formed by R₁₈ and R₁₉ in Formula (3) as R₁₃ is preferably C₃₋₅cycloalkenyl.

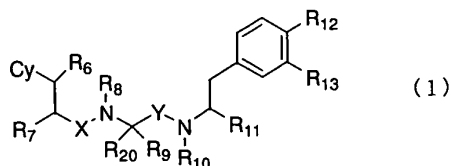
While R₁₃ has the definitions set forth above, R₁₃ is preferably isopropyl, tert-butyl, 1,1-dimethylpropyl and
10 1,1-dimethyl-2-propenyl, with tert-butyl being more preferred.

X is preferably carbonyl or methylene.

Y is preferably carbonyl or methylene.

Examples of compounds of Formula (1)

15



wherein:

Cy, R₆, R₇, R₈, R₉, R₂₀, R₁₀, R₁₁, R₁₂, R₁₃, X and Y are as defined as above

20 include those compounds of which Cy is a group of Formula (2) in which at least one of R₁, R₂, R₃, R₄ and R₅ is halogen and the others are hydrogen or hydroxy; R₆ is hydrogen or methyl; R₇ is hydrogen or optionally substituted amino; R₈ is hydrogen or methyl; R₉ is methyl, isopropyl, isobutyl, sec-butyl, tert-butyl, 3-pentyl, neopentyl, cyclohexyl,
25 phenyl, benzyl, para-hydroxybenzyl, para-fluorobenzyl or

cyclohexylmethyl; R₂₀ is hydrogen; R₁₀ is hydrogen or methyl; R₁₁ is methyl, hydroxymethyl, carbamoylmethyl, methanesulfonylmethyl, ureidemethyl, sulfamoylaminomethyl, methanesulfonylaminomethyl, carbamoyl, methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, isopropylcarbamoyl, cyclopropylcarbamoyl, tert-butylcarbamoyl, 2-pyridylcarbamoyl, methanesulfonylmethylcarbamoyl, methoxymethylcarbamoyl, methoxycarbamoyl, 1-morpholinylcarbonyl, 4-carboxymethyl-1-piperazinecarbonyl, 4-ethoxycarbonylmethyl-1-piperazinecarbonyl, 4-methylsulfonyl-1-piperazinecarbonyl, 2-thiazolyl, 1,3,4-oxadiazol-2-yl, 1,2,4-oxadiazol-5-yl, 1,3,4-triazol-2-yl or 6-methyl-4-pyrimidinon-2-yl; R₁₂ is hydroxy; R₁₃ is isopropyl, tert-butyl (tBu), 1,1-dimethylpropyl or 1,1-dimethyl-2-propenyl. More preferred compounds are Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, Phe(3,4-F₂)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide, N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrilamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea, N-(2-(2-(2-amino-3-(4-fluorophenyl)propanoyl-N-methylamino)-3-methyl)butyrilamino)-3-(3-tert-butyl-4-hydroxyphenyl)propyl)sulfamide, N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2-[N-(4-fluorophenyl)alaninoyl)methylamino]-3-methylbutanamide,

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FOI 61205860

- 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidemethylethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid
- 5 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide, 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol, 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-
- 10 methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide, 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid
- 15 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide, Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH₂, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH₂, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH₂, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-
- 20 25

- tBu)-NH₂, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH₂, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH₂, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH₂, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHtBu, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH₂SO₂CH₃, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHET,
- 10 N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHET, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHET, Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH₂OH, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH₂OH, N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH₂OH, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHET, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHET, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHET, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH₂OH, N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH₂OH, N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH₂OH, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHET, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHET, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHET, Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH₂OH, N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH₂OH, N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH₂OH, Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHcPr and Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHnPr Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHlPr.
- 20
- 25 Particularly preferred compounds are Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, Phe(3,4-F₂)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHET, 2-((2-amino-3-(4-

5

fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid

methanesulfonylmethylethylamide and 2-(2-((2-amino-3-(4-

butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol.

10

Various protected functional groups are defined in Formulae

[illegible]

15

R₇' include those which are known as useful protecting

benzyloxycarbonyl, t-butoxycarbonyl, 9-

20

trimethylsilyl, t-butyldimethylsilyl, benzyl,

of the protecting groups of the protected substituent of

25

benzyloxycarbonyl, t-butoxycarbonyl, 9-

acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl,

known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, 5 trimethylsilyl, t-butyldimethylsilyl, benzyl and benzyloxymethyl. Examples of the protecting groups of the optionally protected hydroxy as R," include those which are known as useful protecting groups of hydroxy; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-10 fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, trimethylsilyl, t-butyldimethylsilyl, benzyl, benzyloxymethyl, t-butyl and tetrahydropyranyl.

Examples of the protecting groups of the protected 15 substituent of the straight-chained or branched C₁₋₃alkyl as R₁₁' include those which are known as useful protecting groups of amino or hydroxy; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, 20 acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl, benzyloxymethyl, t-butyl and tetrahydropyranyl.

Examples of the protecting groups of amine as P₁ include those which are known as useful protecting groups 25 of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-

butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the protected amino of the straight-chained or branched C_{1-3} alkyl as R_{11} ''' include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyl-
dimethylsilyl, benzyl and benzyloxymethyl.

10 Examples of the protecting groups of the optionally protected carboxyl as P_2 include those which are known as useful protecting groups of carboxyl; specific examples are methyl, ethyl, t-butyl, allyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl and t-butyl-
dimethylsilyl.

15 Examples of the protecting groups of amine as P_3 include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyl-
dimethylsilyl, benzyl and benzyloxymethyl.

25 Examples of the protecting groups of the protected amino of the straight-chained or branched C_{1-3} alkyl as R_{11} ''' include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-

butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the optionally protected carboxyl as P₄ include those which are known as useful protecting groups of carboxyl; specific examples are methyl, ethyl, t-butyl, allyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl and t-butyldimethylsilyl.

Examples of the protecting groups of amine as P₅ include those which are known as useful protecting groups of amino; specific examples are benzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethyloxycarbonyl, allyloxycarbonyl, benzoyl, acetyl, trifluoroacetyl, benzenesulfonyl, p-toluenesulfonyl, trimethylsilyl, t-butyldimethylsilyl, benzyl and benzyloxymethyl.

Examples of the protecting groups of the optionally protected carboxyl as P₆ include those which are known as useful protecting groups of carboxyl; specific examples are methyl, ethyl, t-butyl, allyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl and t-butyldimethylsilyl.

Salt-forming acids include inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as acetic acid, oxalic acid, maleic acid, fumaric acid, citric acid, succinic acid, tartaric acid, methanesulfonic acid and trifluoroacetic acid.

The compounds of the present invention can occur as optical isomers and the respective optical isomers and mixtures thereof are all included within the scope of the invention.

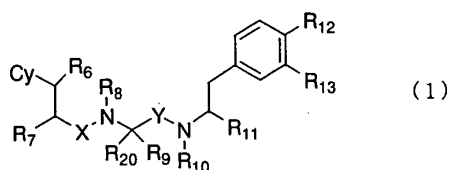
The compounds of the present invention can also be obtained as hydrates.

The subject application claims priority on the basis of Japanese Patent Application Nos. 11-20523 and 11-283163
5 all disclosures in their specification shall be incorporated herein by reference.

On the pages that follow, the present invention is described more specifically and the amino acids that constitute peptides, the amino acids protected by
10 protecting groups, the protecting groups, reagents and solvents are represented by the following abbreviations:
Val: valine, Phe: phenylalanine, Tyr: tyrosine, Z: benzyloxycarbonyl, Boc: tert-butoxycarbonyl, CMPI: 2-chloro-1-methylpyridinium iodide, PyCIU: chloro-N,N,N',N'-
15 bis(tetramethylene)formamidinium hexafluorophosphate, DIC: N,N'-diisopropylcarbodiimide, HOBT: 1-hydroxylbenzotriazole monohydrate, NMM: N-methylmorpholine, TEA: triethylamine, DIEA: diisopropylethylamine, TFA: trifluoroacetic acid, THF: tetrahydrofuran, DMF: N,N-dimethylformamide, CH:
20 chloroform, MC: methylene chloride, M: methanol, N: concentrated aqueous ammonia, EA: ethyl acetate, H and nHx: n-hexane and ACT: acetone.

BEST MODE FOR CARRYING OUT THE INVENTION

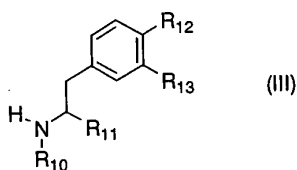
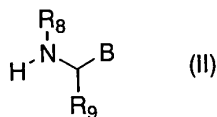
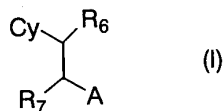
25 The compounds of Formula (1)



wherein C_y , R_6 , R_7 , R_8 , R_9 , R_{20} , R_{10} , R_{11} , R_{12} , R_{13} , X and Y are as defined above

5 can basically be produced by binding Compound (I), Compound (II) and Compound (III), which are represented by the following formulae and in which functional groups other than those involved in bond formation are protected as required:

10



15 A and B in Formulae (I) to (III) are functional groups
which can form a bond by the reaction with amino; specific
examples are carboxyl, formyl, halomethylene of which
halogen is chlorine, bromine or iodine, and
sulfonyloxymethylene of which sulfonyl is methanesulfonyl,
20 trifluoromethanesulfonyl, paratoluenesulfonyl and the like.
 R_1 to R_{10} , R_{12} and R_{13} are as defined above, provided that

when they are reactive groups such as amino, hydroxy or carboxyl, they are protected by normally used appropriate protecting groups, if desired. R_{11} is as defined above or is a functional group which is convertible to one of the
 5 above defined groups.

The compounds of Formula (1) may be produced by first binding Compound (II) and Compound (III), optionally followed by deprotection, and then binding the resultant compound with Compound (I), optionally followed by
 10 deprotection or conversion of the functional group(s). Alternatively, the compound of Formula (1) may be produced by first binding Compound (I) and Compound (II), optionally followed by deprotection, and then binding the resultant compound with Compound (III), optionally followed by
 15 deprotection or conversion of the functional group(s).

The compounds of the present invention may be produced by either the solid-phase process or the liquid-phase process. In the production by the solid-phase process, an automatic organic synthesizer can be used but
 20 it may be replaced by the manual procedure.

Almost all amino acids that are used for the production of the compounds of the present invention are commercially available and readily purchasable. Those which are not commercially available can be produced by
 25 well-known established methods such as the Strecker synthesis, the Bucherer method, the acetamido malonic ester method, the method of alkylating an amino group protected glycine ester and the Z- α -phosphonoglycine trimethylester

method.

Compound (I), if it has a functional group such as amino and hydroxy, with the functional group being protected, is carboxylic acid (A is $-\text{CO}_2\text{H}$), aldehyde (A is $-\text{CHO}$), alkylhalide (A is $-\text{CH}_2\text{-Hal}$), sulfonate (A is $-\text{CH}_2\text{-OSO}_2\text{R}$) or the like. In this case, bond can be formed by reacting A of Compound (I) with the amino group of Compound (II).

Compound (II) can, in almost all cases, be derived from an α -amino acid and B is carboxyl ($-\text{CO}_2\text{H}$), formyl ($-\text{CHO}$), halomethyl ($-\text{CH}_2\text{-Hal}$), sulfonyloxymethyl ($\text{RSO}_2\text{O-CH}_2\text{-}$) or the like. The amino group of Compound (II) is reacted with A of Compound (I) to form bond and B of Compound (II) is reacted with the amino group of Compound (III) to form bond.

Compound (III) is an ethylamine derivative and can be generally derived from an amino acid. The amino group of Compound (III) is reacted with B of Compound (II) to form bond.

When A or B is carboxyl, various methods known in peptide synthesis may be used to activate the carboxyl for condensation with the amino group and such methods include the use of benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), the use of PyCIU, the use of bromo tripyrrolidino phosphonium hexafluorophosphate (PyBrop), the use of chlorotripyrrolidino phosphonium hexafluorophosphate (PyClop), the use of O-(7-azabenzotriazol-1-yl)-1,1,3,3-

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tetramethyluronium hexafluorophosphate (HATU), the use of
DIC, the use of N-ethyl-N'-3-dimethylaminopropyl
carbodiimide (WSCl), the use of dicyclohexyl carbodiimide
(DCC), the use of diphenylphosphorylazide (DPPA), the use
5 of CMPI, the use of 2-bromo-1-methylpyridinium iodide
(BMPI), the combination of one of these reagents with HOBT
or N-hydroxysuccinimide (HONSu), the mixed acid anhydride
method using isobutyl chloroformate or the like, the method
of changing the carboxyl group to a pentafluorophenyl ester
10 (OPfp), a p-nitrophenyl ester (ONP) or an N-
hydroxysuccinimide ester (OSu), and the combination of one
of these methods with HOBT. If necessary, a base such as
TEA, DIEA, NMM or 4-dimethylaminopyridine (DMAP) may be
added to accelerate the reaction.

15 When A or B is formyl, bond can be formed by
conventional reductive bond forming reaction with amino
group. When A or B is halomethylene or
sulfonyloxymethylene, bond can be formed by substitution
reaction with amino group.

20 The compounds of the present invention can also be
produced by applying the specific methods of production to
be described in the following Examples.

On the pages that follow, the production of the
compounds of the invention is described more specifically
25 by reference to Examples, to which the invention is by no
means limited.

In order to demonstrate the utility of the compounds
of the invention, typical examples of them were subjected

to pharmacological tests on the motilin receptor
antagonistic action and the results are described under
Test Examples. The chemical structural formulae or
chemical names of the compounds produced in Examples are
5 set forth in Tables A-1 to A-10 and Tables B-1 to B-18.

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Table A-1

Example No.	Structural formula or chemical name
1	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
2	Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
3	Phe(3,4-F ₂)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
4	Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
5	Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
6	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHSO ₂ Me TFAsalt
7	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe
8	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric 2-(3-tertbutyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoylethylamide
9	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrilamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea
10	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrilamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine
11	N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrilamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-cyano-N''-methylguanidine
12	2-(2-(2-amino-3-(4-fluorophenyl)propanoyl-N-methylamino)-3-methyl)butyrilamino)-3-(3-tertbutyl-4-hydroxyphenyl)propylsulfamide

Table A-2

Example No.	Structural formula or chemical name
13	2-(2-(2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methyl)butyrylamino)-3-(3-tertbutyl-4-hydroxyphenyl)propylaminoacetamide
14	N-[2-(3-tertbutyl-4-hydroxyphenyl)-1-(methanesulfonylaminoethyl)-2-[N-(4-fluorophenylalaninoyl)methylamino]-3-methylbutanamide
15	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidemethylethylamide
16	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide
17	2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butylamino)-3-(3-tBu-4-hydroxyphenyl)propanol
18	(2-(2-(2-amino-3-(4-fluorophenyl)propylamino)-3-methyl-butylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone
19	2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butylamino)-2-(3-tertbutyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone
20	5-(1-(2-((2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tertbutyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione
21	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

Table A-3

Example	Structural formula or chemical name
No.	
22	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide
23	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tertbutyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide
24	2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide
25	2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tertbutyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

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Table A-4

Example No.	Structural formula or chemical name
26	Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
27	Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
28	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH ₂
29	N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH ₂
30	N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH ₂
31	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe
32	N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe
33	N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe
34	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
35	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
36	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe
37	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe
38	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe
39	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH ₂
40	N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH ₂
41	N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH ₂
42	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe
43	N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe
44	N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe
45	Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH ₂
46	N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH ₂
47	N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH ₂
48	Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe
49	N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe
50	N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe

Table A-5

Example No.	Structural formula or chemical name
51	Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH ₂
52	N-Me-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NH ₂
53	N-Et-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NH ₂
54	Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe
55	N-Me-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NHMe
56	N-Et-Phe(4-F)-N-Et-Val- N-Me-Tyr(3-tBu)-NHMe
57	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH ₂
58	N-Me-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NH ₂
59	N-Et-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NH ₂
60	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHMe
61	N-Me-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NHMe
62	N-Et-Phe(4-F)-N-Et-Val- N-Et-Tyr(3-tBu)-NHMe
63	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHtBu
64	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH ₂ SO ₂ CH ₃
65	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide
66	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide
67	2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide
68	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-ethyl-3-methylbutanamide
69	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide
70	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide

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Table A-6

Example No.	Structural formula or chemical name
71	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide
72	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide
73	2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide
74	2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide
75	2-((2-amino-3-(4-fluorophenyl)propyl)-N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide
76	2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide
77	2-((2-amino-3-(4-fluorophenyl)propyl)-N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-N,3-dimethylbutanamide
78	2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(1-aminomethyl-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-3-methylbutanamide

Table A-7

Example No.	Structural formula or chemical name
101	Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NH ₂ t
102	N-Me-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NH ₂ t
103	N-Et-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NH ₂ t
104	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂ t
105	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂ t
106	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂ t
107	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH ₂ t
108	N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH ₂ t
109	N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH ₂ t
110	Phe(4-F)-N-Et-Val -Tyr(3-tBu)-NH ₂ t
111	N-Me-Phe(4-F)-N-Et-Val -Tyr(3-tBu)-NH ₂ t
112	N-Et -Phe(4-F)-N-Et-Val -Tyr(3-tBu)-NH ₂ t
113	Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH ₂ t
114	N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH ₂ t
115	N-Et-Phe(4-F)-N-Et-Val-Me-Tyr(3-tBu)-NH ₂ t
116	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH ₂ t
117	N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH ₂ t
118	N-Et-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH ₂ t
119	Phe(4-F)-N-Me-Val- Tyr(3-t Bu)-NH-n-Pr
120	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH-i-Pr
121	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t Bu)-NH-c-Pr
122	Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH ₂ OH
123	N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH ₂ OH
124	N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH ₂ OH
125	N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH ₂ OH

Table A-8

Example No.	Structural formula or chemical name
126	N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH ₂ OH
127	Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH ₂ OH
128	N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH ₂ OH
129	N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH ₂ OH
130	Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHCH ₂ OH
131	N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHCH ₂ OH
132	Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH ₂ OH
133	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-((1S)-1-[[3-(tert-butyl)-4-hydroxyphenyl]methyl]-2-morpholin-4-yl)-2-oxoethyl)-3-methyl-N-methylbutanamide
134	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-((1S)-1-[[3-(tert-butyl)-4-hydroxyphenyl]methyl]-2-[4-(methylsulfonyl)piperazinyl]-2-oxoethyl)-3-methyl-N-methylbutanamide
135	ethyl 2-[4-((2S)-2-((2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-3,N-dimethylbutanoylamino)-3-[3-(tert-butyl)-4-hydroxyphenyl]propanol)piperazinyl]acetate
136	2-[4-((2S)-2-((2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-3,N-dimethylbutanoylamino)-3-[3-(tert-butyl)-4-hydroxyphenyl]propanol)piperazinyl]acetic acid
137	Phe(4-F)-N-Me-Val-N-Pr-Tyr(3-tBu)-NH ₂
138	Phe(4-F)-N-Me-Abu-N-Me-Tyr(3-tBu)-NH ₂
139	Phe(4-F)-N-Me-D-Abu-N-Me-Tyr(3-tBu)-NH ₂
140	Phe(4-F)-N-Me-Nva-N-Me-Tyr(3-tBu)-NH ₂

[illegible]

Example No.	Structural formula or chemical name
141	Phe(4-F)-N-Me-D-Nva-N-Me-Tyr(3-tBu)-NH ₂
142	Phe(4-F)-N-Me-Ile-N-Me-Tyr(3-tBu)-NH ₂
143	Phe(4-F)-N-Me-D-Ile-N-Me-Tyr(3-tBu)-NH ₂
144	Phe(4-F)-N-Me-Leu-N-Me-Tyr(3-tBu)-NH ₂
145	Phe(4-F)-N-Me-D-Leu-N-Me-Tyr(3-tBu)-NH ₂
146	(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-N-methylpent-4-enamide
147	(2R)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanolyamino]-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-N-methylpent-4-enamide
148	Phe(4-F)-N-Me-Leu(γ-Me)-N-Me-Tyr(3-tBu)-NH ₂
149	Phe(4-F)-N-Me-D-Leu(γ-Me)-N-Me-Tyr(3-tBu)-NH ₂
150	Phe(4-F)-N-Me-Ala(β-CF ₃)-N-Me-Tyr(3-tBu)-NH ₂
151	Phe(4-F)-N-Me-Chg-N-Me-Tyr(3-tBu)-NH ₂
152	Phe(4-F)-N-Me-D-Chg-N-Me-Tyr(3-tBu)-NH ₂
153	Phe(4-F)-N-Me-Cha-N-Me-Tyr(3-tBu)-NH ₂
154	Phe(4-F)-N-Me-D-Cha-N-Me-Tyr(3-tBu)-NH ₂
155	Phe(4-F)-N-Me-Phe-N-Me-Tyr(3-tBu)-NH ₂
156	Phe(4-F)-N-Me-D-Phe-N-Me-Tyr(3-tBu)-NH ₂
157	Phe(4-F)-N-Me-Phe(4-F)-N-Me-Tyr(3-tBu)-NH ₂
158	Phe(4-F)-N-Me-D-Phe(4-F)-N-Me-Tyr(3-tBu)-NH ₂
159	Phe(4-F)-N-Me-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH ₂
160	Phe(4-F)-N-Me-D-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH ₂
161	Phe(4-F)-N-Me-Tyr-N-Me-Tyr(3-tBu)-NH ₂
162	Phe(4-F)-N-Me-D-Tyr-N-Me-Tyr(3-tBu)-NH ₂
163	Phe(4-F)-N-Me-Ala(β-2-thienyl)-N-Me-Tyr(3-tBu)-NH ₂

Table A-10

Example No.	Structural formula or chemical name
164	Phe(4-F)-N-Me-D-Ala(β -2-thienyl)-N-Me-Tyr(3-tBu)-NH ₂
165	Phe(4-F)-N-Me-Ala(β -c-Pr)-N-Me-Tyr(3-tBu)-NH ₂
166	Phe(4-F)-N-Me-Phg-N-Me-Tyr(3-tBu)-NH ₂
167	Phe(4-F)-N-Me- α -Me-Phe-Tyr(3-tBu)-NH ₂
168	Phe(4-F)-N-Me- α -Me-Phe-Tyr(3-tBu)-NH ₂
169	Phe(4-F)-N-Me- α -Me-Leu-Tyr(3-tBu)-NH ₂
170	Phe(4-F)-N-Me- α -Me-D-Abu-Tyr(3-tBu)-NH ₂
171	Phe(4-F)-N-Me- α -Me-D-Val-Tyr(3-tBu)-NH ₂
172	(2S)-N-[(N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]carbamoyl)cyclopentyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide
173	(2S)-N-[(N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]carbamoyl)cyclohexyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide
174	Phe(4-F)-N-Me-Tle-Tyr(3-tBu)-NH ₂
175	Phe(4-F)-N-Me-Tle-N-Me-Tyr(3-tBu)-NH ₂
176	Phe(4-F)-N-Me-D-Phg-N-Me-Tyr(3-tBu)-NH ₂
177	(2S)-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-2-[2-amino-3-(2-fluoro-4-pyridyl)-N-methylpropanoylamino]-3-methyl-N-methylbutanamide
178	(2S)-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-2-[2-amino-3-(2-fluoro-5-pyridyl)-N-methylpropanoylamino]-3-methyl-N-methylbutanamide
179	(2S)-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-2-[2-amino-N-methyl-3-[4-(trifluoromethyl)phenyl]propanoylamino]-3-methyl-N-methylbutanamide
180	(2S)-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-2-[2-[(4-fluorophenyl)methyl]-3-hydroxy-N-methylpropanoylamino]-3-methyl-N-methylbutanamide
181	Ala(β -4-pyridyl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
182	Phe(4-CN)-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂
183	Trp-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂

Table B-1

Example No.	Structural formula
1	
2	
3	
4	
5	

Table B-2

Example No.	Structural formula
6	
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9	
10	
11	

Table B-3

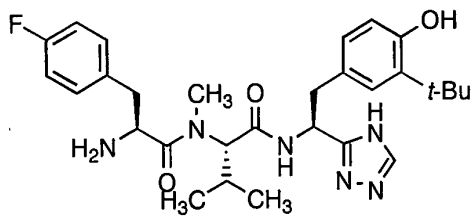
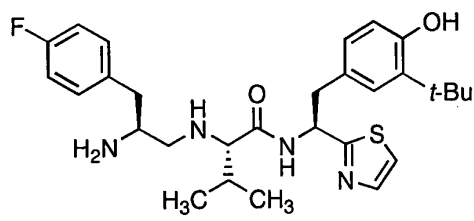
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13	
14	
15	
16	
17	

Table B-4

Example No.	Structural formula
18	
19	
20	
21	
22	
23	

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Table B-5

Example No.	Structural formula
24	
25	

5 Table B-6

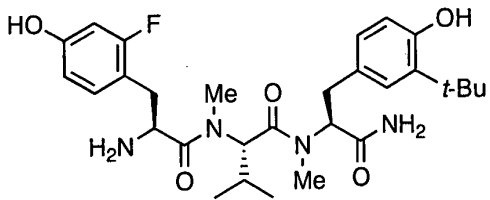
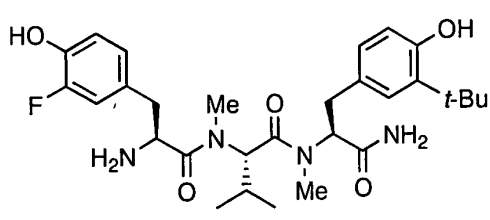
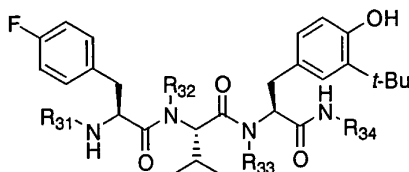
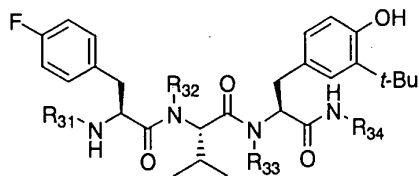
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27	

Table B-7



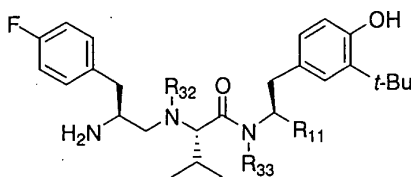
Example No.	R ₃₁	R ₃₂	R ₃₃	R ₃₄	Example No.	R ₃₁	R ₃₂	R ₃₃	R ₃₄
28	H	Me	H	H	54	H	Et	Me	Me
29	Me	Me	H	H	55	Me	Et	Me	Me
30	Et	Me	H	H	56	Et	Et	Me	Me
31	H	Me	H	Me	57	H	Et	Et	H
32	Me	Me	H	Me	58	Me	Et	Et	H
33	Et	Me	H	Me	59	Et	Et	Et	H
34	Me	Me	Me	H	60	H	Et	Et	Me
35	Et	Me	Me	H	61	Me	Et	Et	Me
36	H	Me	Me	Me	62	Et	Et	Et	Me
37	Me	Me	Me	Me	101	H	Me	H	Et
38	Et	Me	Me	Me	102	Me	Me	H	Et
39	H	Me	Et	H	103	Et	Me	H	Et
40	Me	Me	Et	H	122	H	Me	H	CH ₂ OH
41	Et	Me	Et	H	123	Me	Me	H	CH ₂ OH
42	H	Me	Et	Me	124	Et	Me	H	CH ₂ OH
43	Me	Me	Et	Me	104	H	Me	Me	Et
44	Et	Me	Et	Me	105	Me	Me	Me	Et
45	H	Et	H	H	106	Et	Me	Me	Et
46	Me	Et	H	H	132	H	Me	Me	CH ₂ OH
47	Et	Et	H	H	125	Me	Me	Me	CH ₂ OH
48	H	Et	H	Me	126	Et	Me	Me	CH ₂ OH
49	Me	Et	H	Me	107	H	Me	Et	Et
50	Et	Et	H	Me	108	Me	Me	Et	Et
51	H	Et	Me	H	109	Et	Me	Et	Et
52	Me	Et	Me	H	127	H	Me	Et	CH ₂ OH
53	Et	Et	Me	H	128	Me	Me	Et	CH ₂ OH
					129	Et	Me	Et	CH ₂ OH

Table B-8



Example No.	R ₃₁	R ₃₂	R ₃₃	R ₃₄
110	H	Et	H	Et
111	Me	Et	H	Et
112	Et	Et	H	Et
113	H	Et	Me	Et
114	Me	Et	Me	Et
115	Et	Et	Me	Et
116	H	Et	Et	Et
117	Me	Et	Et	Et
118	Et	Et	Et	Et
130	H	Et	Et	CH ₂ OH
131	Me	Et	Et	CH ₂ OH
121	H	Me	Me	cPr
119	H	Me	H	nPr
120	H	Me	H	iPr
137	H	Me	nPr	H
63	H	Me	H	tBu
64	H	Me	Me	CH ₂ SO ₂ CH ₃

Table B-9



5

Example No.	R ₃₂	R ₃₃	R ₁₁	Example No.	R ₃₂	R ₃₃	R ₁₁
65	H	Me	CONH ₂	72	Me	Me	Me
66	Me	Me	CONH ₂	73	Ac	Me	Me
67	Ac	Me	CONH ₂	74	H	H	Me
68	H	Et	CONH ₂	75	Me	H	Me
69	H	H	CH ₂ OH	76	Ac	H	Me
70	Me	H	CH ₂ OH	77	Me	Me	CH ₂ OH
71	H	Me	Me	78	Me	H	CH ₂ NH ₂

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Table B-10

Example No.	Structural formula
133	
134	
135	
136	
138	
139	

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Table B-11

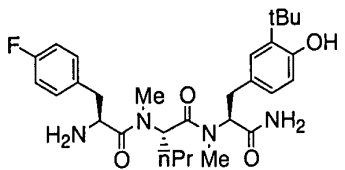
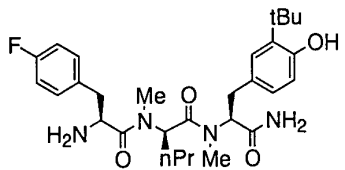
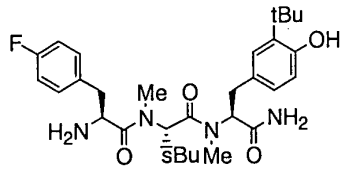
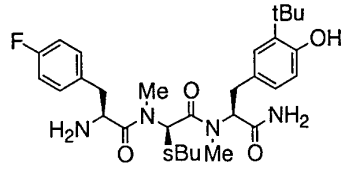
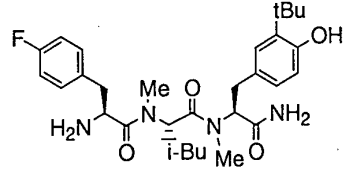
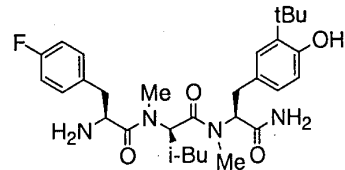
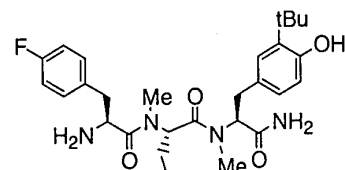
Example No.	Structural formula
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141	
142	
143	
144	
145	
146	

Table B-12

Example No.	Structural formula
147	
148	
149	
150A, 150B	
151	
152	

Table B-13

Example No.	Structural formula
153	
154	
155	
156	
157	

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Table B-14

Example No.	Structural formula
158	
159	
160	
161	
162	

00000219 121304
T02121 61206360

Table B-15

Example No.	Structural formula
163	
164	
165	
166	
167	
168	

000003 131301
FOI# 64206860

Table B-16

Example No.	Structural formula
169	
170	
171	
172	
173	
174	

Table B-17

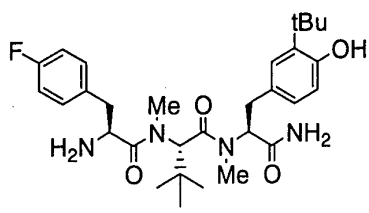
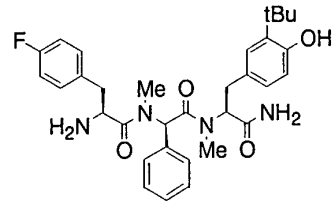
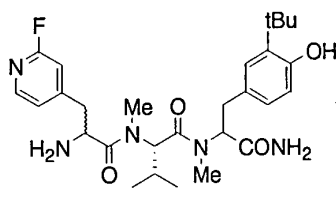
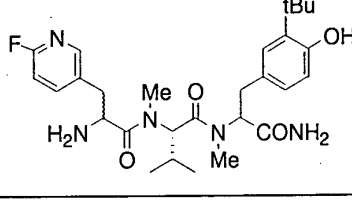
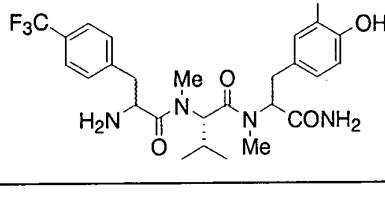
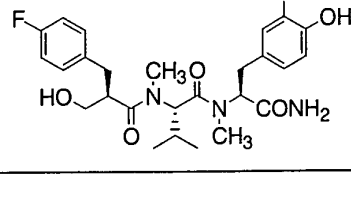
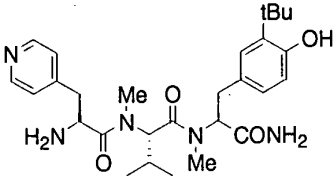
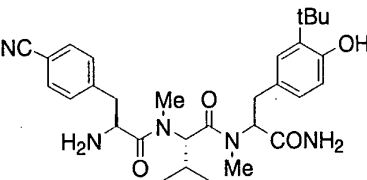
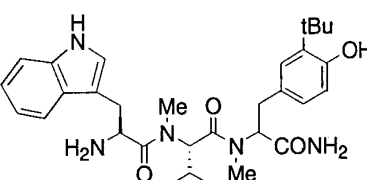
Example No.	Structural formula
175	
176	
177A, 177B	
178A, 178B	
179A, 179B	
180A, 180B	

Table B-18

Example No.	Structural formula
181	
182	
183	

0000019 121201

In the following Examples, Merck Silica gel 60 (0.063-0.200 mm) or Merck Silica gel 60 (0.040-0.063 mm) was used for silica gel column chromatography unless otherwise stated.

- 5 In the following examples, mass spectra (MA) and ¹H-NMR were taken by the following equipment:
MA (EI-MS): SHIMADZU GCMS-QP5050A or SHIMADZU GCMS-QP1000.
MA (ESI-MS): Extrel ELQ400
MA (FAB-MS): JASCO 70-250SEQ

- 10 ¹H-NMR: JEOL JNM-EX-270 (270 MHz) or Bruker ARX300 (300 MHz)

- Reaction conditions, data from the equipment, yielded amount and the like of Example 28 onward were shown in Tables in which "Reaction time" means stirring time and
15 "Column sol." means the eluting solvent for silica gel column chromatography.

 In the following Examples, the retention time (min.) on HPLC is measured under the following conditions:

- Apparatus: HITACHI L-6300 or Young Lin M930
20 Column: μ BONDASPHERE 5 μ C18 100A (3.9 \times 150 mm)
Detecting conditions: linear gradient of B (10-80%) using A (0.1% TFA/distilled water) and B (0.1% TFA/acetonitrile), 35 min., flow of rate 1 ml/min, detected at 280 nm (UV).

25 Example 1

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

(1) Synthesis of Tyr(3-tBu)-OMe

To a solution of Tyr-OMe·HCl (500 g, 2.16 mol) in

¹H-NMR(CDCl₃): δ 1.36(9H,s), 3.04(2H,brd,J=5.6Hz),
3.72(3H,s), 4.57-4.68(1H,m), 4.97(1H,brs), 5.10(2H,s),
5.20(1H,brd,J=7.9Hz), 6.55(1H,d,J=7.9Hz),
6.78(1H,dd,J=7.9,2.0Hz), 6.95(1H,d,J=2.0Hz), 7.26-
5 7.41(5H,m)

(3) Synthesis of Z-Phe(3-tBu-4-benzyloxy)-OMe

A solution of Z-Tyr(3-tBu)-OMe (1.0 g, 2.60 mmol),
benzyl bromide (0.56 ml, 4.68 mmol) and potassium carbonate
(1.08 g, 7.79 mmol) in DMSO (5 ml) was stirred overnight.

10 The resulting mixture was mixed with a saturated aqueous
ammonium chloride solution, extracted with ethyl acetate.
The organic layer was washed with water and then saturated
brine, dried over anhydrous magnesium sulfate and
evaporated to remove the solvent under reduced pressure;
15 the thus obtained residue was subjected to silica gel
column chromatography (developing solvent: ethyl acetate:n-
hexane = 1:5) to give Z-Phe(3-tBu-4-benzyloxy)-OMe (1.44 g,
99%).

¹H-NMR(CDCl₃): δ 1.36(9H,s), 3.05(2H,d,J=5.6Hz), 3.71(3H,s),
20 4.60-4.68(1H,m), 5.06(2H,s), 5.09(2H,s),
5.24(1H,brd,J=8.3Hz), 6.82(1H,d,J=8.5Hz),
6.88(1H,dd,J=8.5,1.8Hz), 7.00(1H,d,J=1.8Hz), 7.27-
7.50(10H,m)

(4) Synthesis of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH₂

25 To a solution of Z-Phe(3-tBu-4-benzyloxy)-OMe (1.44 g,
2.60 mmol) in 1,4-dioxane (30 ml), a 2N aqueous sodium
hydroxide solution (3 ml) was added and stirred for 2 hours.
The resulting mixture was mixed with water and washed with

ethyl acetate; the aqueous layer was rendered acidic by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Z-Phe(3-tBu-4-benzyloxy)-OH (1.35 g).

To a solution of the thus obtained crude Z-Phe(3-tBu-4-benzyloxy)-OH (1.35 g) in THF (7 ml), under cooling with ice, methyl iodide (1.3 ml, 20.8 mmol) was added and then sodium hydride (60% in oil, 312 mg, 7.8 mmol) was added slowly, followed by stirring for 21 hours at room temperature. The resulting mixture was mixed with water, rendered acidic by the addition of dilute hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (1.60 g).

To a solution of the thus obtained crude Z-N-Me-
20 Phe(3-tBu-4-benzyloxy)-OH (1.60 g) in THF (25 ml), under
cooling with ice, ethyl chloroformate (0.27 ml, 2.86 mmol)
and NMM (0.31 ml, 2.86 mmol) were added in that order. The
mixture was stirred for 15 min. and further stirred for
another 15 min. while bubbling gaseous ammonia therein.
25 The resultant mixture was left standing at room temperature,
diluted with ethyl acetate and washed with water and then
saturated brine. The organic layer was dried over
anhydrous magnesium sulfate and evaporated to remove the

solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1) to give Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH₂ (1.08 g, 88%, in 3 steps).

5 ¹H-NMR(CDCl₃): δ 1.37(9H,s), 2.87(3H,s), 2.86-2.99(1H,m), 3.21-3.35(1H,m), 4.73-4.95(1H,m), 5.06(2H,s), 5.09(2H,s), 5.67,5.83 and 6.13(3/2H,brs), 6.78-7.47(27/2H,m)

(5) Synthesis of N-Me-Tyr(3-tBu)-NH₂

To a solution of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH₂ (1.08 g, 2.28 mmol) in methanol (20 ml), 10% palladium/carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was
15 subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1) to give N-Me-Tyr(3-tBu)-NH₂ (0.55 g, 96%).

¹H-NMR(CDCl₃): δ 1.40(9H,s), 2.31(3H,s), 2.63(1H,dd,J=14.7,10.7Hz), 3.10-3.19(2H,m), 5.24(1H,brs),
20 5.38(1H,brs), 6.63(1H,d,J=7.9Hz), 6.91(1H,dd,J=7.9,1.8Hz), 7.05(1H,brs), 7.10(1H,d,J=1.8Hz)

(6) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

To a solution of Z-N-Me-Val-OH (700 mg, 2.64 mmol), N-Me-Tyr(3-tBu)-NH₂ (0.55 g, 2.20 mmol) and CMPI (674 mg, 2.64 mmol) in THF (22 ml), under cooling with ice, TEA (0.61 ml) was added and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed
25

with saturated brine, dried over sodium sulfate and
 evaporated to remove the solvent under reduced pressure;
 the thus obtained residue was subjected to silica gel
 column chromatography (developing solvent: ethyl acetate:n-
 5 hexane = 3:2) to give Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.98
 g, 90%).

¹H-NMR(CDCl₃):(four rotamers) δ 0.07, 0.32, 0.63, 0.74,
 0.79, 0.81, 0.84 and 0.89(6H,d,J=6.3-6.6Hz), 1.30, 1.33,
 1.37 and 1.39(9H,s), 2.13-2.33(1H,m), 2.34, 2.41, 2.78,
 10 2.87 and 2.98(6H,s), 2.79-3.22(2H,m), 4.40 and
 4.32(1H,d,J=10.6Hz), 4.60-5.43(5H,m), 5.96(1H,brs),
 6.23-7.12(3H,m), 7.26-7.47(5H,m)

(7) Synthesis of N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (Intermediate
 I-b3 in the following Tables)

15 A mixture of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.98 g,
 1.97 mmol) and 20% palladium hydroxide/carbon (0.10 g) in
 methanol (20 ml) was stirred at room temperature in a
 hydrogen atmosphere for 1.5 hours. The reaction mixture
 was filtered and the filtrate was concentrated under
 20 reduced pressure; the thus obtained residue was subjected
 to silica gel column chromatography (developing solvent:
 chloroform:methanol:aqueous ammonia = 100:10:1) to give
 N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.71 g, 99%).

¹H-NMR(CDCl₃):(two rotamers) δ 0.35,0.71,0.92 and
 25 0.96(6H,d,J=6.9Hz), 1.36 and 1.37(9H,s), 1.73-1.81 and
 2.03-2.17(1H,m), 1.74 and 2.23(3H,s), 2.64(1H,d,J=9.2Hz),
 2.90-3.04(1H,m), 2.93 and 3.00(3H,s), 3.19 and
 4.60(1H,dd,J=14.7,5.8 and 10.7,3.8Hz), 5.29,5.32 and

6.06(2H,brs), 5.59(1H,dd,J=10.4,5.8Hz), 6.54 and
6.60(1H,d,J=7.9Hz), 6.79 and 6.93(1H,dd,J=7.9,2.0 and
1.7Hz), 7.01 and 7.07(1H,d,J=2.0 and 1.7Hz), 8.10(1H,brs)

(8) Synthesis of Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

5 To a solution of Z-Phe(4-F)-OH (1.09 g, 3.44 mmol),
N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (1.04 g, 2.87 mmol) and CMPI
(878 mg, 3.44 mmol) in THF (30 ml), TEA (0.96 ml, 6.88
mmol) was added under cooling with ice and stirred at room
temperature overnight. The reaction mixture was mixed with
10 water and extracted with ethyl acetate. The organic layer
was washed with saturated brine, dried over anhydrous
magnesium sulfate and evaporated to remove the solvent
under reduced pressure; the thus obtained residue was
subjected to silica gel column chromatography (developing
15 solvent: n-hexane:ethyl acetate =1:3) to give Z-Phe(4-F)-N-
Me-Val-N-Me-Tyr(3-tBu)-NH₂ (1.73 g, 91%).

¹H-NMR(CDCl₃):(two rotamers) δ 0.57,0.73,0.75 and
0.90(6H,d,J=6.3-6.6Hz), 1.33 and 1.39(9H,s), 2.18-
3.43(5H,m), 2.40 and 3.03(3H,s), 2.74 and 3.01(3H,s),
20 4.62-5.49(7H,m), 5.95(1H,brs), 6.44(1H,d,J=7.9Hz), 6.57-
7.35(12H,m)

(9) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

A mixture of Z-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂
(1.73 g, 2.61 mmol) and 10% palladium/carbon (340 mg) in
25 methanol (50 ml) was stirred at room temperature in a
hydrogen atmosphere for 17 hours. The reaction mixture was
filtered and the filtrate was concentrated under reduced
pressure; the thus obtained residue was subjected to silica

gel column chromatography (developing solvent:
chloroform:methanol:aqueous ammonia = 100:10:1) to give
Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (1.25 g, 91%).

EI-MS:528(M⁺)

- 5 ¹H-NMR(CDCl₃):(two rotamers) δ 0.50,0.76,0.79 and
0.93(6H,d,J=6.3-6.9Hz), 1.34 and 1.39(9H,s), 2.19-
2.95(5H,m), 2.50 and 3.03(3H,s), 2.81 and 3.02(3H,s), 3.17
and 3.34(1H,dd,J=15.2,5.9 and 13.9,6.9Hz), 3.66 and
3.84(1H,dd,J=8.9,4.6 and 8.6,4.6Hz), 4.91 and
10 5.07(1H,d,J=10.6Hz), 5.07,5.19,5.30,5.98 and 6.64(2H,brs),
5.49(1H,dd,J=10.6,5.9Hz), 6.35 and 6.62(1H,d,J=7.9Hz),
6.74(2/3H,dd,J=7.9,1.7Hz), 6.95-7.11(19/3H,m)

Example 2

- 15 Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂
(1) Synthesis of Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

- To a solution of Boc-Phe(4-Cl)-OH (354 mg, 1.18 mmol),
N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.33 g, 0.908 mmol) and CMPI
(301 mg, 1.18 mmol) in THF (8 ml), TEA (0.38 ml, 2.72 mmol)
20 was added under cooling with ice and stirred at room
temperature overnight. The reaction mixture was mixed with
water and extracted with ethyl acetate. The organic layer
was washed with saturated brine, dried over anhydrous
magnesium sulfate and evaporated to remove the solvent
25 under reduced pressure; the thus obtained residue was
subjected to silica gel column chromatography (developing
solvent: chloroform:methanol:aqueous ammonia = 40:1:0.05)
to give Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.45 g,

77%).

(2) Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

To a solution of Boc-Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.45 g, 0.697 mmol) in methylene chloride (4 ml),
5 TFA (3 ml) was added, stirred for 20 min. and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with a saturated aqueous NaHCO₃ solution, and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and
10 evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 30:1:0.1) to give Phe(4-Cl)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (355 mg, 93%).

15 EI-MS: 544 and 546(M⁺)

¹H-NMR(CDCl₃): (two rotamers) δ 0.49, 0.75, 0.78 and 0.93(6H, d, J=6.3-6.9Hz), 1.34 and 1.38(9H, s), 2.10-2.92(5H, m), 2.50 and 3.04(3H, s), 2.80 and 3.01(3H, s), 3.13 and 3.33(1H, dd, J=15.2, 5.9 and 13.9, 6.9Hz), 3.67 and
20 3.85(1H, dd, J=8.9, 5.0 and 8.6, 5.0Hz), 4.90 and 5.06(1H, d, J=10.6Hz), 5.33, 5.41, 5.99 and 6.61(2H, brs), 5.49(1H, dd, J=10.6, 5.9Hz), 6.37 and 6.63(1H, d, J=7.9Hz), 6.72 and 6.98(1H, dd, J=7.9, 1.7Hz), 7.07-7.10(3H, m), 7.25-7.31(2H, m)

25

Example 3

Phe(3,4-F₂)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

(1) Synthesis of Fmoc-Phe(3,4-F₂)-N-Me-Val-N-Me-Tyr(3-tBu)-

NH₂

To a solution of Fmoc-Phe(3,4-F₂)-OH (500 mg, 1.18 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.33 g, 0.908 mmol) and CMPI (301 mg, 1.18 mmol) in THF (8 ml), TEA (0.38 ml, 2.72 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05), giving Fmoc-Phe(3,4-F₂)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.56 g, 80%).

(2) Synthesis of Phe(3,4-F₂)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

To a solution of Fmoc-Phe(3,4-F₂)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.55 g, 0.715 mmol) in methylene chloride (5 ml), diethylamine (5 ml) was added, stirred for 4 hours and then evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:ethanol:aqueous ammonia = 60:1:0.1) to give Phe(3,4-F₂)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (381 mg, 97%).

EI-MS: 546(M⁺)

¹H-NMR(CDCl₃): (two rotamers) δ 0.51, 0.74, 0.79 and 0.93(6H, d, J=6.3-6.9 Hz), 1.33 and 1.38(9H, s), 2.10-2.93(5H, m), 2.51 and 3.03(3H, s), 2.83 and 3.01(3H, s), 3.17 and 3.33(1H, dd, J=14.8, 5.9 and 13.9, 6.6 Hz), 3.66 and

3.84(1H,dd,J=8.4,5.0 and 8.6,4.3Hz), 4.88 and
5.07(1H,d,J=10.6Hz), 5.41, 5.9(1H,brs), 5.41-5.51(1H,m),
6.43 and 6.64(1H,d,J=7.9Hz), 6.75(2/5H,dd,J=7.9,1.7Hz),
6.84-7.16(28/5H,m)

5

Example 4

Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

(1) Synthesis of Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

To a solution of Boc-Phe(3-F)-OH (0.20 g, 0.706 mmol),
10 N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.21 g, 0.578 mmol) and CMPI
(0.20 g, 0.783 mmol) in THF (6 ml), TEA (0.30 ml, 2.15
mmol) was added under cooling with ice and stirred at room
temperature overnight. The reaction mixture was mixed with
water and extracted with ethyl acetate. The organic layer
15 was washed with saturated brine, dried over anhydrous
magnesium sulfate and evaporated to remove the solvent
under reduced pressure; the thus obtained residue was
subjected to silica gel column chromatography (developing
solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05)
20 to give Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.33 g,
91%).

(2) Synthesis of Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

To a solution of Boc-Phe(3-F)-N-Me-Val-N-Me-Tyr(3-
tBu)-NH₂ (0.33 g, 0.525 mmol) in methylene chloride (3 ml),
25 TFA (1.5 ml) was added, stirred for 15 min. and then
evaporated to remove the solvent under reduced pressure.
The residue was mixed with methylene chloride, washed with
a saturated aqueous NaHCO₃ solution, dried over anhydrous

magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1) to give Phe(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (241 mg, 87%).

EI-MS:528(M⁺)

¹H-NMR(CDCl₃):(two rotamers) δ 0.51,0.73,0.78 and 0.93(6H,d,J=6.3-6.6Hz), 1.33 and 1.38(9H,s), 2.10-2.96(5H,m), 2.46 and 3.03(3H,s), 2.78 and 3.01(3H,s), 3.16 and 3.35(1H,dd,J=14.8,5.9 and 13.9,6.6Hz), 3.70 and 3.90(1H,dd,J=8.3,5.6 and 8.6,5.0Hz), 4.89 and 5.06(1H,d,J=10.6Hz), 5.42, 5.99(1H,brs), 5.43-5.52(1H,m), 6.41 and 6.64(1H,d,J=7.9Hz), 6.72(2/5H,dd,J=7.9,1.7Hz), 6.83-6.99(18/5H,m), 7.10(2/5H,d,J=1.7Hz), 7.22-7.33(1H,m)

15

Example 5

Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

(1) Synthesis of Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

To a solution of Boc-Phe(2-F)-OH (0.20 g, 0.706 mmol), N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.21 g, 0.578 mmol) and CMPI (0.20 g, 0.783 mmol) in THF (6 ml), TEA (0.30 ml, 2.15 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing

25

solvent: chloroform:methanol:aqueous ammonia = 60:1:0.05)
to give Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.33 g,
91%).

(2) Synthesis of Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

5 To a solution of Boc-Phe(2-F)-N-Me-Val-N-Me-Tyr(3-
tBu)-NH₂ (0.33 g, 0.525 mmol) in methylene chloride (3 ml),
TFA (1.5 ml) was added, stirred for 15 min. and then
evaporated to remove the solvent under reduced pressure.
The residue was mixed with methylene chloride, washed with
10 a saturated aqueous NaHCO₃ solution, dried over anhydrous
magnesium sulfate and evaporated to remove the solvent
under reduced pressure. The thus obtained residue was
subjected to silica gel column chromatography (developing
solvent: chloroform:methanol:aqueous ammonia = 40:1:0.1) to
15 give Phe(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (235 mg, 85%).

EI-MS: 528(M⁺)

¹H-NMR(CDCl₃): (two rotamers) δ 0.45, 0.71, 0.79 and
0.93(6H, d, J=5.9-6.6Hz), 1.31 and 1.38(9H, s), 2.10-
2.89(5H, m), 2.47 and 3.06(3H, s), 2.76 and 3.01(3H, s), 3.14
20 and 3.34(1H, dd, J=14.3, 5.9 and 13.9, 6.6Hz), 3.79 and
3.95(1H, dd, J=8.4, 5.0 and 8.6, 4.3Hz), 4.88 and
5.06(1H, d, J=10.6Hz), 5.37, 5.99(1H, brs), 5.41-5.51(1H, m),
6.43(3/5H, d, J=7.9Hz), 6.56(2/5H, brs), 6.60-6.71(1H, m),
6.92-7.29(6H, m)

25

Example 6

TFA salt of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂SO₂Me

(1) Synthesis of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH₂SO₂Me

To a solution of crude Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (0.95 g, 2.0 mmol), WSCI·HCl (0.77 g, 3.99 mmol) and methanesulfonamide (0.29 g, 3.0 mmol) in DMF (15 ml), DMAP (0.49 g, 0.99 mmol) was added under cooling with ice and stirred at room temperature overnight. The mixture was mixed with water and then with 2N hydrochloric acid, extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1) to give the titled compound (0.83 g, 75%).

¹H-NMR(CDCl₃): δ 1.36(9H,s), 2.80(s,3H), 2.97-3.30(m,2H), 3.21(s,3H), 4.60-4.74(m,1H), 5.08(s,2H), 5.13(s,2H), 6.81(d,1H,J=8.2Hz), 6.86-7.13(m,2H), 7.20-7.46(m,10H), 9.0(brs,1H)

(2) Synthesis of Z-N-Me-Val-N-Me-Tyr(3-t-Bu)-NH₂SO₂Me

A mixture of Z-N-Me-Tyr(3-tBu-4-benzyloxy)-NH₂SO₂Me (0.80 g, 1.45 mmol) and 20% palladium hydroxide/carbon (0.09 g) in methanol (15 ml) was stirred at room temperature overnight in a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated to remove the solvent under reduced pressure, giving crude N-Me-Tyr(3-t-Bu)-NH₂SO₂Me (0.53 g).

To a solution of the crude N-Me-Tyr(3-t-Bu)-NH₂SO₂Me (0.51 g, 1.43 mmol), Z-N-Me-Val-OH 0.49 g, 1.86 mmol) and CMPI (0.51 g, 2.00 mmol) in THF (10 ml), TEA (0.60 ml, 4.29

mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water, rendered acidic by the addition of 2N hydrochloric acid and extracted with ethyl acetate. The organic layer
5 was washed with saturated brine, dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:3 containing 0.5% acetic acid) to give
10 the titled compound (0.70 g, in 2 steps, 85%).

(3) Synthesis of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-Bu)-NHSO₂Me

A mixture of Z-N-Me-Val-N-Me-Tyr(3-t-Bu)-NHSO₂Me (0.65 g, 1.13 mmol) and 20% palladium hydroxide/carbon
15 (0.09 g) in methanol (10 ml) was stirred at room temperature for 2.5 hours in a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was evaporated to remove the solvent under reduced pressure, giving crude N-Me-Val-N-Me-Tyr(3-t-Bu)-NHSO₂Me (0.50 g).

20 To a solution of the above crude compound (0.48 g, 1.09 mmol), Boc-Phe(4-F)-OH 0.40 g, 1.41 mmol) and CMPI (0.39 g, 1.53 mmol) in THF (8 ml), TEA (0.46 ml, 3.27 mmol) was added under cooling with ice and stirred at room temperature overnight for 22 hours. The reaction mixture
25 was mixed with water, rendered acidic by the addition of 10% aqueous citric acid solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over magnesium sulfate and evaporated to remove the

solvent under reduced pressure; the thus obtained residue
was subjected to silica gel column chromatography
(developing solvent: ethyl acetate:n-hexane = 2:3
containing 5% acetic acid) to give the titled compound
5 (0.50 g, in 2 steps, 65%).

(4) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-Bu)-NH₂Me
TFA salt

To a solution of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t-
Bu)-NH₂Me (208 mg, 0.294 mmol) in methylene chloride (6
10 ml), TFA (3 ml) was added and stirred for 1.5 hours. The
reaction mixture was evaporated under reduced pressure; the
thus obtained residue was dissolved in a mixture of
acetonitrile/water (1:10) (80 ml), which mixture containing
0.1% TFA, and lyophilized to give the titled compound (0.20
15 g, 94%).

EI-MS:606(M⁺)

¹H-NMR(DMSO-d₆):(three rotamers) δ 0.02(d,3/5H,J=5.9Hz),
0.22(d,3/5H,J=5.9Hz), 0.62(d,3/5H,J=7.6Hz),
0.68(d,3/5H,J=6.6Hz), 0.77(d,9/5H,J=6.6Hz),
20 0.89(d,9/5H,J=6.3Hz), 1.28(s,27/5H), 1.31(s,9/5H),
1.35(s,9/6H), 1.86-2.03(m,2/7H), 2.15-2.28(m,5/7H), 2.5-
3.4(m,10H), 4.35-4.62(m,1H), 4.80-5.02(1H), 5.11-5.42(m,1H),
6.55-7.18(m,7H), 8.0-8.2(m,3H), 8.98-9.06(m,1H),
11.2(brs,1H)

25

Example 7

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

(1) Synthesis of Z-N-Me-Phe(4-benzyloxy-3-tBu)-NHOMe

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To a solution of Z-N-Me-Phe(4-benzyloxy-3-tBu)-OH (3.8 g, 7.99 mmol) in THF (50 ml), ethyl chloroformate (0.85 ml, 8.78 mmol) was added under cooling with ice and then NMM (0.97 ml, 8.78 mmol) was slowly added dropwise. After stirring for 1 hour, MeONH₂ (1.0 g, 12.0 mmol) and TEA 2.23 ml (16.0 mmol) were added to the mixture, followed by stirring for 2 hours at room temperature. The mixture was mixed with water, and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2) to give the titled compound (2.7 g, 67%).

¹H-NMR(CDCl₃): δ 1.39(9H,s), 2.95(3H,s), 2.99(1H,m), 3.24(1H,m), 3.64(3H,s), 4.7(1H,m), 5.1(4H,d), 6.8-7.5(13H,m), 9.06(1H,s)

(2) Synthesis of N-Me-Tyr(3-tBu)-NHOMe

To a solution of Z-N-Me-Phe(4-benzyloxy-3-tBu)-NHOMe (2.7 g, 5.36 mmol) in MeOH (30 ml), palladium hydroxide /carbon (675 mg) was added and stirred in a hydrogen atmosphere for 2 hours. Insoluble matters were removed by filtration with Celite and the filtrate was concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 20:1) to give the titled compound (1.24 g, 82%).

¹H-NMR(CDCl₃): δ 1.43(9H,s), 2.45(3H,s), 2.92(2H,m), 3.12(1H,m), 3.59(3H,s), 6.77(1H,d,J=9.4Hz),

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layer was dried over anhydrous sodium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (972 mg, 56%).

(6) Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe

To a solution of Boc-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHOMe (972 mg, 1.508 mmol) in methylene chloride (10 ml), TFA (7 ml) was added and stirred for 30 min. The mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 20:1), giving the titled compound (288 mg, 34%).

15 EI-MS: 558 (M^+)

1H -NMR ($CDCl_3$): δ 0.42 (3H, d, $J=13.5$ Hz), 0.79 (3H, d, $J=13.2$ Hz), 1.33 (9H, s), 2.10 (1H, m), 2.60 (1H, m), 2.90 (2H, m), 2.91 (3H, s), 3.07 (3H, s), 3.28 (1H, m), 3.68 (3H, s), 3.91 (1H, m), 4.82 (1H, d, $J=10.7$ Hz), 5.13 (1H, m), 6.60 (1H, d, $J=10.4$ Hz), 6.89 (1H, m), 7.0-7.3 (5H, m), 9.1 (1H, m)

Example 8

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

(1) Synthesis of N-benzyloxycarbonyl-3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide

To a solution of Z-Tyr(3-tBu)-OH (3.04 g, 8.19 mmol)

in THF (8.2 ml), under cooling with ice N,N-carboxyldiimidazole (1.59 g, 9.83 mmol) was added and stirred for 1 hour. To the mixture, 2-aminopyridine (925 mg, 9.83 mmol) was then added and stirred for 2 hours under
5 cooling with ice and then further 6.5 hours at room temperature. The mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure.

10 The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (2.16 g, 59%).

¹H-NMR(CDCl₃): δ 1.24(9H,s), 2.95-3.20(2H,m), 4.45-4.60(1H,m), 5.11(2H,dd,J=17.5,12.2Hz), 6.53(1H,d,J=7.9Hz),
15 6.85(1H,d,J=7.9Hz), 6.95-7.15(2H,m), 7.32(5H,brs), 7.67-7.73(1H,m), 8.15-8.25(2H,m)

(2) Synthesis of 3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide

To a solution of N-benzyloxycarbonyl-3-tert-butyl-4-hydroxyphenylalanyl (2-pyridyl)amide (2.16 g, 4.83 mmol) in
20 methanol (160 ml), 10% palladium/carbon (400 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. After filtering the reaction mixture, the filtrate was evaporated to remove the solvent under reduced
25 pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 10:1:100), giving the titled compound (1.48 g, 98%).

¹H-NMR(CDCl₃): δ 1.36(9H,s), 2.72-3.23(2H,m), 3.67-
3.72(1H,m), 6.62(1H,d,J=7.9Hz), 6.85-6.88(1H,m), 6.95-
7.20(2H,m), 7.70-7.77(1H,m), 8.29-8.39(2H,m)

(3) Synthesis of 2-(N-benzyloxycarbonyl-N-methylamino)-3-
5 methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-
pyridylcarbamoyl)ethylamide

To a solution of 3-tert-butyl-4-hydroxyphenylalanyl
(2-pyridyl)amide (1.48 g, 4.73 mmol), Z-N-Me-Val-OH (1.63 g,
6.15 mmol) and CMPI (1.57 g, 6.15 mmol) in THF 30 ml, TEA
10 (1.5 ml, 10.88 mmol) was added under cooling with ice and
stirred for 3 hours under cooling with ice. The mixture
was mixed with water and extracted with ethyl acetate. The
organic layer was washed with saturated brine, dried over
anhydrous magnesium sulfate and evaporated to remove the
15 solvent under reduced pressure; the thus obtained residue
was subjected to silica gel column chromatography
(developing solvent: ethyl acetate:n-hexane = 1:2), giving
the titled compound (1.74 g, 65%).

¹H-NMR(CDCl₃): δ 0.70-0.95(6H,m), 1.26(9H,s), 2.20-
20 2.35(1H,m), 2.70-3.10(5H,m), 4.00-4.20(1H,m), 4.65-
4.80(1H,m), 5.17(2H,brs), 6.44(1H,d,J=7.6Hz), 6.60-6.85(1H,
m), 6.95-7.10(2H,m), 7.36(5H,brs), 7.60-7.75(1H,m), 8.10-
8.25(2H,m)

(4) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-
25 tert-butyl-4-hydroxyphenyl)-1-(2-
pyridylcarbamoyl)ethylamide

To a solution of 2-(N-benzyloxycarbonyl-N-
methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-

hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide (1.74 g, 3.10 mmol) in methanol (50 ml), 10% palladium carbon (300 mg) was added and stirred in a hydrogen atmosphere at room temperature overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 5:0.1:100), giving the titled compound (1.30 g, 98%).

¹H-NMR(CDCl₃): δ 0.69(3H,d,J=6.9Hz), 0.85(3H,d,J=6.9Hz), 1.31(9H,s), 1.95-2.11(1H,m), 2.36(3H,s), 2.81(1H,d,J=4.6Hz), 2.99-3.18(2H,m), 4.73-4.81(1H,m), 6.59(1H,d,J=7.9Hz), 6.94(1H,dd,J=7.9,2.0Hz), 7.00-7.10(2H,m), 7.65-7.72(1H,m), 7.80(1H,d,J=7.9Hz), 8.18(1H,d,J=8.6Hz), 8.25(1H,d,J=4.6Hz),

(5) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid
2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(2-pyridylcarbamoyl)ethylamide (1.25 g, 2.93 mmol), Boc-Phe(4-F)-OH (1.08 g, 3.81 mmol) and CMPI (973 mg, 3.81 mmol) in THF 19 ml, TEA (0.94 ml, 6.74 mmol) was added under cooling with ice and stirred for 4 hours under cooling with ice. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure;

2.44(1H,m), 2.50-3.25(4H,m), 2.78(2.4H,s), 2.85(0.6H,s),
3.55-3.65(0.8H,m), 3.80-3.90(0.2H,m), 4.00(0.8H,d,J=10.9Hz),
4.36(0.2H,d,J=10.9Hz), 4.65-4.80(0.2H,m), 4.90-5.00(0.8H,m),
6.55-7.20(8H,m), 7.65-7.75(1H,m), 8.15-8.25(2H,m)

5

Example 9

N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

10 (1) Synthesis of Z-3-tBu-tyrosinol

To a solution of Z-Tyr(3-tBu)-OMe (7.4 g, 19 mmol) in THF (190 ml), lithium borohydride (1.25 g, 57.4 mmol) was added under cooling with ice and stirred for 1.5 hours at room temperature. The mixture was mixed with a saturated aqueous NH₄Cl solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (6.8 g, 99%).

¹H-NMR(CDCl₃): δ 1.38(9H,s), 2.15(1H,m), 2.78(2H,brd,J=6.9Hz), 3.5-3.8(2H,m), 3.8-4.0(1H,m), 4.86(1H,s), 4.9-5.0(1H,m), 5.09(2H,s), 6.58(1H,d,J=7.9Hz), 6.88(1H,brd,J=7.9Hz), 7.05(1H,brs), 7.34(5H,s)

(2) Synthesis of 2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine

To a solution of Z-3-tBu-tyrosinol (2 g, 5.6 mmol),

triphenylphosphine (1.76 g, 6.7 mmol), phthalimide (0.99 g, 6.7 mmol) in THF 50 ml, diethyl azodicarboxylate (DEAD) (1.05 ml, 6.7 mmol) was added under cooling with ice and stirred at the same temperature for 1 hour. The mixture

5 was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography

10 (developing solvent: hexane:ethyl acetate = 2:1) to give (1-(1,3-dihydro-1,3-dioxo-isoindol-2-yl)methyl-2-(3-tBu-4-hydroxyphenyl)ethyl)carbamic acid benzyl ester (3.2 g).

To the above compound (3.2 g), a 40% methylamine methanol solution (40 ml) was added at room temperature and

15 stirred at the same temperature for 10 hours. The reaction mixture was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the

20 titled compound (1.9 g).

¹H-NMR(CDCl₃): δ 1.37(9H,s), 2.6-2.9(4H,m), 3.7-3.9(4/5H,m), 3.9-4.1(1/5H,m) 4.8-4.9(4/5H,m), 5.09(2H,s), 5.4-5.5(1/5H,m), 6.5-6.6(1H,m), 6.84(1H,d,J=7.3Hz), 6.9-7.1(1H,m), 7.33(5H,s)

25 (3) Synthesis of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

A mixture of 2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine (1.0 g, 2.8 mmol), potassium

cyanate (0.5 g, 5.5 mmol), acetic acid (0.5 ml), dioxane (10 ml) and water (10 ml) was stirred at 60°C for 2 hours. The mixture was mixed with a saturated aqueous NaHCO₃ solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:methanol = 50:1), giving the titled compound (0.9 g, 80%).

¹H-NMR(CD₃OD): δ 1.35(9H,s), 2.5-2.8(2H,m), 3.0-3.2(1H,m), 3.2-3.4(1H,m), 3.7-3.9(1H,m), 5.01(2H,d,J=3.6Hz), 6.63(1H,d,7.9Hz), 6.84(1H,brd,J=7.9Hz), 7.04(1H,brs), 7.2-7.4(5H,m)

(4) Synthesis of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

To a solution of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.9 g, 2.26 mmol) in methanol (20 ml), 10% palladium carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature for 12 hours. After filtration, the filtrate was concentrated under reduced pressure to give N-(2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.54 g).

To a solution of the above compound (0.53 g, 2 mmol), Z-N-Me-Val-OH (0.69 g, 2.6 mmol) and CMPI (0.67 g, 2.6 mmol) in THF (20 ml), TEA (1 ml, 7.2 mmol) was added under cooling with ice and stirred at room temperature for 1.5 hours. The reaction mixture was mixed with water and

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extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel

5 column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (0.98 g, 98%).

$^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.82(3H,d,J=6.3Hz), 0.88(3H,d,J=6.3Hz), 1.35(9H,s), 2.1-2.3(1H,m), 2.6-2.8(2H,m), 2.76(3H,s),
10 3.0-3.4(2H,m), 3.9-4.1(1H,m), 4.7-5.0(2H,m), 5.0-5.1(2H,m), 5.5-5.6(1H,m), 6.4-7.0(5H,m), 7.34(5H,s)

(5) Synthesis of N-(2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

15 To a solution of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.97 g, 1.95 mmol) in methanol (20 ml), 10% palladium carbon (100 mg) was added and stirred in a hydrogen atmosphere at room temperature for 3
20 hours. After filtering the reaction mixture, the filtrate was evaporated to remove the solvent under reduced pressure, giving N-(2-(2-amino-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea (0.72 g).

To a solution of the above crude compound (0.64 g, 1.85 mmol), Boc-Phe(4-F)-OH (0.63 g, 2.22 mmol) and CMPI (0.57 g, 2.23 mmol) in THF (18 ml), TEA (0.93 ml, 6.67 mmol) was added under cooling with ice and stirred at room temperature for 8 hours. The mixture was mixed with water

and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel

5 column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (0.79 g, 66%).

¹H-NMR(DMSO-d₆): δ 0.70, 0.75, 0.85, and 0.95(total 6H,d,J=5.9-6.3Hz), 1.2-1.4(18H,m), 2.0-2.1(1H, m),
10 2.4-2.9(7H,m), 2.9-3.1(2H,m), 3.8-4.0(1H,m), 4.3-4.6(2H,m), 5.39, 5.51(2H,brs), 5.74(1H,d,J=1.3Hz), 5.9-6.0(1H,m), 6.6-6.9(2H,m), 6.9-7.1(2H,m), 7.1-7.3(3H,m), 7.60 and 7.73(total 1H, brd), 9.02(1H,s)

(6) Synthesis of N-(2-(2-((2-amino-3-(4-
15 fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea

To a solution of N-(2-(2-((2-(t-butoxycarbonylamino)-
3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)urea
20 (0.75 g) in methylene chloride (6 ml), TFA (6 ml) was added under cooling with ice, stirred at room temperature for 1 hour and evaporated to remove the solvent under reduced pressure. The thus obtained residue was mixed with methylene chloride, washed with a saturated aqueous NaHCO₃
25 solution, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent:

chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (480 mg, 76%).

FAB-MS: 544 ($M^+ + 1$)

$^1\text{H-NMR}$ (DMSO- d_6): δ 0.49, 0.73, and 0.85 (total 6H, d, $J=6.0$ -
5 6.6 Hz), 1.30 and 1.32 (total 9H, s), 2.0-2.2 (1H, m), 2.4-
3.1 (9H, m), 3.7-4.1 (3H, m), 4.52 and 5.48 (total 2H, m),
5.8-6.0 (1H, m), 6.6-6.8 (2H, m), 6.9-7.3 (5H, m), 7.67 and
8.79 (total 1H, d, $J=7.6$ -8.6 Hz), 9.01 and 9.06 (total 1H, s)

10 Example 10

N-(2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine

(1) Synthesis of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-
15 hydroxyphenyl)propyl)carbamic acid t-Bu ester

To a solution of (2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)amine (1.46 g, 4.1 mmol) in dioxane (8 ml), an aqueous sodium carbonate solution (0.44 g, 4.1 mmol) (8 ml) and $(\text{Boc})_2\text{O}$ (0.9 g, 4.1 mmol) were
20 added in that order under cooling with ice and stirred at the same temperature for 2.5 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under
25 reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (1.7 g, 91%).

¹H-NMR(CDCl₃):δ 1.38(9H,s), 1.42(9H,s), 2.6-2.9(2H,m),
3.1-3.3(2H,m), 3.8-4.0(1H,m), 4.7-4.8(1H,m), 5.08(2H,s),
6.58(1H,d,J=8.9Hz), 6.85(1H,brd,J=8.9Hz), 7.03(1H,brs),
7.2-7.5(5H,m)

- 5 (2) Synthesis of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester

To a solution of N-(2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.6 g,
10 3.5 mmol) in methanol (35 ml), 10% palladium carbon (160 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1.5 hours. After filtration, the filtrate was concentrated under reduced pressure to give N-((2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu
15 ester (1.1 g).

To a solution of the thus obtained crude compound (1.1 g, 3.42 mmol), Z-N-Me-Val-OH (1.08 g, 4.08 mmol) and CMPI (1.04 g, 4.07 mmol) in THF (35 ml), TEA (1.7 ml, 12.2 mmol) was added under cooling with ice and stirred at room
20 temperature for 1 hour. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica
25 gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (1.8 g, 93%).

¹H-NMR(CDCl₃):δ 0.82(3H,d,J=6.6Hz), 0.90(3H,d,J=6.2Hz),
1.37(9H,s), 1.42(9H,s), 2.1-2.3(1H,m), 2.5-2.8(5H,m), 3.0-

3.3(2H,m), 3.9-4.3(2H,m), 5.13(2H,s), 6.44(1H,d,J=7.9Hz),
6.75(1H,brd,J=7.9Hz), 7.00(1H,brs), 7.36(5H,s)

(3) Synthesis of N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-

5 methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester

To a solution of N-(2-(2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.8 g, 3.16
10 mmol) in methanol (35 ml), 10% palladium carbon (180 mg) was added and stirred for 1 hour in a hydrogen atmosphere at room temperature. After filtration, the filtrate was concentrated under reduced pressure to give N-(2-(2-(N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.33 g).
15

To a solution of the thus obtained crude compound (1.33 g, 3.15 mmol), Z-Phe(4-F)-OH (1.2 g, 3.78 mmol) and CMPI (0.97 g, 3.78 mmol) in THF (35 ml), TEA (1.6 ml, 11.5 mmol) was added under cooling with ice and stirred at room
20 temperature for 10 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica
25 gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (1.48 g, 53%).

¹H-NMR(CDCl₃):δ 0.68, 0.75, 0.91, and 0.98(total 6H,d,J=6.2-6.9Hz), 1.35,1.37,1.40, and 1.42(total 18H,m),

2.1-3.4(10H,m), 4.0-4.5, 4.7-5.1, and 5.5-5.7(total 7H,m),
6.3-7.5(17H, m)

(4) Synthesis of 2-(2-((2-(benzyloxycarbonylamino)-3-(4-
fluorophenyl)propionyl)-N-methylamino)-3-

5 methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine

To a solution of N-(2-(2-((2-
(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-
methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-
hydroxyphenyl)propyl)carbamic acid t-Bu ester (1.38 g) in
10 methylene chloride (5 ml), TFA (5 ml) was added under
cooling with ice, stirred at room temperature for 30 min.
and evaporated under reduced pressure to remove the solvent.
The thus obtained residue was mixed with methylene chloride,
washed with a saturated aqueous NaHCO₃ solution, dried over
15 anhydrous magnesium sulfate and evaporated to remove the
solvent under reduced pressure; the thus obtained residue
was subjected to silica gel column chromatography
(developing solvent: chloroform:methanol:aqueous ammonia =
20:1:0.1), giving the titled compound (1.1 g, 92%).

20 ¹H-NMR(CDCl₃):δ 0.67,0.76,0.92,and 0.97(total 6H,d,J=6.6-
6.9Hz), 1.35 and 1.37(total 9H,s), 2.2-2.5(1H,m), 2.4-
3.1(9H,m), 4.0-4.2 and 4.4-4.5(total 2H,m), 4.7-5.1(2H,m),
5.5-5.6 and 5.7-5.9(total 1H,brd,J=7.6-8.1Hz), 6.2-6.4,
6.5-6.7, and 6.8-7.4(total 13H,m)

25 (5) Synthesis of N-(2-(2-((2-amino-3-(4-
fluorophenyl)propionyl)-N-methylamino)-3-
methylbutyrylamino)-3-(3-tBu-4-
hydroxyphenyl)propyl)guanidine

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To a solution of 2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine (580 mg, 0.91 mmol) in DMF (4.5 ml), 1H-pyrazole-1-carboxamide hydrochloride (161 mg, 1.09 mmol) and DIEA (0.19 ml, 1.09 mmol) were added at room temperature and stirred at the same temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (aminopropylated silica gel (CHROMATOREX NH-DM1020, FUJI SILYSIA CHEMICAL LTD.), developing solvent: ethyl acetate:methanol = 100:1 to 10:1) to give N-(2-(2-((2-(benzyloxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)guanidine (410 mg).

To a solution of the above compound (410 mg) in methanol (20 ml), 10% palladium carbon (40 mg) was added and stirred in a hydrogen atmosphere at room temperature for 5 hours. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (aminopropylated silica gel (CHROMATOREX NH-DM1020, FUJI SILYSIA CHEMICAL LTD.), developing solvent: ethyl acetate:methanol = 5:1), giving the titled compound (250 mg, 76%).

FAB-MS: 543($M^+ + 1$)

$^1\text{H-NMR}(\text{CD}_3\text{OD})$: δ 0.47, 0.53, 0.80, 0.90(6H, d, $J=6.3-6.9\text{Hz}$), 1.31, 1.37(9H, s), 2.0-2.3(1H, m), 2.41, 2.46, and 2.57(total

3H,s), 2.5-3.4(6H,m), 3.8-4.6(3H,m), 6.6-7.3(7H,m)

Example 11

Synthesis of N-(2-(2-((2-amino-3-(4-
5 fluorophenyl)propionyl)-N-methylamino)-3-
methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-
cyano-N''-methylguanidine

To a solution of 2-(2-((2-(benzyloxycarbonylamino)-3-
(4-fluorophenyl)propionyl)-N-methylamino)-3-
10 methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propylamine
(500 mg, 0.79 mmol) in ethanol (4 ml), dimethyl N-
cyanodithioiminocarbonate (127 mg, 0.87 mmol) was added at
room temperature and stirred at the same temperature for 16
hours. The reaction mixture was concentrated under reduced
15 pressure; the thus obtained residue was mixed with a 40%
methylamine methanol solution (5 ml) at room temperature
and stirred at the same temperature for 16 hours. The
reaction mixture was concentrated under reduced pressure
and the thus obtained residue was subjected to silica gel
20 column chromatography (developing solvent:
chloroform:methanol:aqueous ammonia = 20:1:0.1) to give N-
(2-(2-((2-(benzyloxycarbonylamino)-3-(4-
fluorophenyl)propionyl)-N-methylamino)-3-
methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)-N'-
25 cyano-N''-methylguanidine (450 mg).

To a solution of the above compound (440 mg) in
methanol (6 ml), 10% palladium carbon (50 mg) was added and
stirred in a hydrogen atmosphere at room temperature for 15

hours. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (280 mg, 78%).

FAB-MS:582(M⁺+1)

¹H-NMR(CDCl₃):δ 0.62, 0.79, 0.87, and 0.91(total 6H,d,J=6.3-6.6Hz), 1.37 and 1.40(total 9H,s), 2.1-2.4(1H,m), 2.5-3.0(10H,m), 3.1-3.4(2H,m), 3.6-4.4(3H,m), 5.8-6.1(1H,m), 6.6-7.2(7H,m), 8.68(1H,d,J=6.6Hz)

Example 12

2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

(1) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylamine (514 mg, 0.811 mmol) in 1,4-dioxane (8 ml), sulfamide (156 mg, 1.62 mmol) was added and stirred at 120°C for 5 hours. The reaction mixture was evaporated under reduced pressure to remove the solvent; the thus obtained residue was mixed with water, and extracted with chloroform. The organic layer was washed

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with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 20:1), giving the titled compound (397 mg, 69%).

$^1\text{H-NMR}(\text{CDCl}_3)$: (two rotamers) δ 0.69, 0.85 and 0.99(6H, d, $J=6.3-6.6\text{Hz}$), 1.36 and 1.37(9H, s), 1.80-1.90(1H, m), 2.22-2.40(1H, m), 2.43 and 2.81(3H, s), 2.60-3.10(4H, m), 3.26-3.38(1H, m), 3.70-3.80(1H, m), 3.90-4.10(1H, m), 4.28-4.44(1H, m), 4.72-5.30(3H, m), 5.03(2H, s), 6.52-6.66(2H, m), 6.80-7.40(10H, m)

(2) Synthesis of 2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide

A mixture of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylsulfamide (332 mg, 0.466 mmol) and 10% palladium carbon (40 mg) in methanol (5 ml) was stirred at room temperature in a hydrogen atmosphere overnight. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 200:10:1), giving the titled compound (180 mg, 67%).

FAB-MS: 580 ($\text{M}+\text{H}^+$)

$^1\text{H-NMR}(\text{CDCl}_3)$: (two rotamers) δ 0.63, 0.75, 0.81 and

0.93(6H,d,J=6.3-6.6Hz), 1.38 and 1.39(9H,s), 2.20-3.42(6H,m), 2.60 and 3.02(3H,s), 3.49(1H,s), 3.60-3.90(2H,m), 4.30-4.44(1H,m), 5.30-5.40(1H,m), 6.56-7.16(7H,m), 8.34-8.42(1H,m)

5

Example 13

2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide

- 10 (1) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetic acid ethyl ester

- To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylamine (1.17 g, 1.84 mmol) in ethanol (18 ml), ethyl glyoxylate (0.7 ml, 2.76 mmol), acetic acid (1.8 ml) and sodium cyanoborohydride (173 mg, 2.76 mmol)
- 15 were added and stirred for 1 hour. The reaction mixture was mixed with a saturated aqueous NaHCO_3 solution, extracted with ethyl acetate and washed with saturated brine. The resultant was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced
- 25 pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate:methylene chloride = 2:3:1), giving the titled compound (900 mg, 68%).

¹H-NMR(CDCl₃): (two rotamers) δ 0.65, 0.75, 0.91 and
0.97(6H, d, J=6.2-6.9Hz), 1.22 and 1.29(3H, t, J=7.2Hz), 1.35
and 1.36(9H, s), 2.22-2.40(1H, m), 2.42 and 2.90(3H, s), 2.60-
3.02(5H, m), 3.22-3.46(2H, m), 4.06-4.28(2H, m),
5 4.47(1H, d, J=12.2Hz), 4.80-5.12(3H, m), 5.29(2H, s),
5.74(1H, d, J=8.9Hz), 6.58-7.42(12H, m)

(2) Synthesis of 2-(2-(2-benzyloxycarbonylamino-3-(4-
fluorophenylpropanoyl-N-methylamino)-3-
methyl)butyrylamino)-3-(3-tert-butyl-4-
10 hydroxyphenyl)propylaminoacetamide

To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-
fluorophenylpropanoyl-N-methylamino)-3-
methyl)butyrylamino)-3-(3-tert-butyl-4-
hydroxyphenyl)propylaminoacetic acid ethyl ester (889 mg,
15 1.23 mmol) in methanol (24 ml), aqueous ammonia (16 ml)
was added and stirred for 15 hours at room temperature.
The reaction mixture was evaporated to remove the solvent
under reduced pressure, extracted with ethyl acetate and
washed with saturated brine. The resultant was dried over
20 anhydrous magnesium sulfate and evaporated to remove the
solvent under reduced pressure; the thus obtained residue
was subjected to silica gel column chromatography
(developing solvent: chloroform:methanol:aqueous ammonia =
110:10:1), giving the titled compound (600 mg, 70%).

25 ¹H-NMR(CDCl₃): (two rotamers) δ 0.65, 0.75, 0.90 and
0.96(6H, d, J=6.0-6.6Hz), 1.36 and 1.37(9H, s), 2.22-
2.40(1H, m), 2.47 and 2.82(3H, s), 2.60-3.02(4H, m), 3.24 and
3.26(2H, s), 4.02-4.38(2H, m), 4.76-5.08(3H, m), 5.40-

5.90(3H,m), 6.56-7.38(12H,m)

(3) Synthesis of 2-(2-(2-amino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide

- 5 To a solution of 2-(2-(2-benzyloxycarbonylamino-3-(4-fluorophenylpropanoyl-N-methylamino)-3-methyl)butyrylamino)-3-(3-tert-butyl-4-hydroxyphenyl)propylaminoacetamide (595 mg, 0.860 mmol) in methanol (10 ml), 20% palladium hydroxide/carbon (150 mg)
- 10 was added and stirred at room temperature in a hydrogen atmosphere overnight. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol:hexane =
- 15 10:1:1), giving the titled compound (333 mg, 70%).

FAB-MS:558(M+H⁺)

- ¹H-NMR(CDCl₃):(two rotamers)δ 0.66,0.79 and 0.92(6H,d,J=6.3-6.6Hz), 1.36 and 1.39(9H,s), 2.22-2.38(1H,m), 2.63 and 2.91(3H,s), 2.50-2.82(4H,m), 3.12-
- 20 3.28(2H,m), 3.58-3.88(2H,m), 4.18-4.40(2H,m), 5.50-5.70(1H,m), 6.58-7.14(8H,m)

Example 14

- N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-2-[N-(4-fluorophenylalaninoyl)methylamino]-3-methylbutanamide
- 25 (1) Synthesis of N-Z-2-(4-benzyloxy-3-tert-butylphenyl)-1-hydroxymethylethylamine

To a solution of Z-Phe(4-benzyloxy-3-tBu)-OME (5.8 g, 12.2 mmol) in methanol/water (100 ml/20 ml), sodium borohydride (1.5 g, 36.6 mmol) was added and stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, mixed with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (5.1 g, 94%).

(2) Synthesis of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropylamine

15 To a solution of N-Z-2-(4-benzyloxy-3-tert-butylphenyl)-1-hydroxymethylethylamine (5.09 g, 11.4 mmol), triphenylphosphine (4.41 g, 17.1 mmol) and phthalimide (2.51 g, 17.1 mmol) in THF (66 ml), diethyl azodicarboxylate (3.0 ml, 17.1 mmol) was added and stirred
20 for 4 hours under cooling with ice. The reaction mixture was concentrated; a solution of the thus obtained residue in methanol (70 ml) was mixed with hydrazine (6 ml) and stirred at room temperature for 4 hours. The reaction mixture was mixed with water and extracted with ethyl
25 acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent:

methylene chloride:methanol = 10:1), giving the titled compound (2.45 g, 49%).

(3) N-[3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropyl]methanesulfonamide

5 To a solution of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropylamine (1.27 g, 2.84 mmol) in methylene chloride (29 ml), TEA (0.6 ml, 4.26 mmol) and then methanesulfonyl chloride (0.3 ml, 3.69 mmol) were added slowly under cooling with ice. After stirring for 30
10 min., the mixture was mixed with water and extracted with chloroform. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene
15 chloride:ethyl acetate:n-hexane = 1:1:2), giving the titled compound (1.23 g, 83%).

(4) Synthesis of 2-[N-(benzyloxycarbonyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide

20 N-[3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylaminopropyl]methanesulfonamide (1.2 g, 2.29 mmol) was dissolved in a mixture of methanol (23 ml) and methylene chloride (5 ml), mixed with palladium hydroxide/carbon (0.60g) and stirred for 12 hours in a
25 hydrogen atmosphere. After filtering off insoluble material using Celite, the filtrate was concentrated to give crude N-[2-amino-3-(4-benzyloxy-3-tert-butylphenyl)propyl]methanesulfonamide (0.68 g).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 1.39(s, 9H), 2.48(dd, 1H, J=8.2, 13.9Hz),
2.73(dd, 1H, J=5.1, 13.3Hz), 2.94(dd, 1H, J=7.9, 11.9Hz),
2.96(s, 3H), 3.10-3.22(m, 1H), 3.24(dd, 1H, J=3.6, 12.2Hz),
6.60(d, 1H, J=7.9Hz), 6.83(dd, 1H, J=2.0, 7.9Hz),
5 7.03(d, 1H, J=2.0Hz)

To a solution of the above crude compound (0.66 g), Z-N-Me-Val-OH (758 mg, 2.86 mmol) and CMPI (730 mg, 2.86 mmol) in THF (22 ml), TEA (0.91 ml, 6.59 mmol) was added under cooling with ice. The resultant was stirred overnight at room temperature, mixed with a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:ethyl acetate:n-hexane = 1:3:2), giving the titled compound (1.08 g, 90%).

(5) Synthesis of 2-[N-(N-benzyloxycarbonyl-4-fluorophenylalaninoyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide

To a solution of 2-[N-(benzyloxycarbonyl)methylamino]-N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-methylbutanamide (1.0 g, 1.83 mmol) in methanol (18 ml), palladium hydroxide/carbon (0.40 g) was added and stirred in a hydrogen atmosphere for 1.5 hours. After filtering off insoluble material using Celite, the filtrate was

concentrated; to a solution of the thus obtained residue
 (0.75 g), Z-Phe(4-F)-OH (748 mg, 2.66 mmol) and CMPI (602
 mg, 2.36 mmol) in THF 18 ml, TEA (0.82 ml, 5.44 mmol) was
 added under cooling with ice. The mixture was stirred at
 5 room temperature overnight, mixed with a saturated aqueous
 sodium bicarbonate solution and extracted with ethyl
 acetate. The organic layer was dried over magnesium
 sulfate and evaporated to remove the solvent under reduced
 pressure; the thus obtained residue was subjected to silica
 10 gel column chromatography (developing solvent: methylene
 chloride:ethyl acetate:n-hexane = 1:3:2), giving the titled
 compound (827 mg, 64%).

(6) Synthesis of N-[2-(3-tert-butyl-4-hydroxyphenyl)-1-
 (methanesulfonylaminomethyl)ethyl]-2-[N-(4-
 15 fluorophenylalaninoyl)methylamino]-3-methylbutanamide

To a solution of 2-[N-(N-benzyloxycarbonyl-4-
 fluorophenylalaninoyl)methylamino]-N-[2-(3-tert-butyl-4-
 hydroxyphenyl)-1-(methanesulfonylaminomethyl)ethyl]-3-
 methylbutanamide (680 mg, 0.95 mmol) in methanol (10 ml),
 20 palladium hydroxide/carbon (0.25 g) was added and stirred
 in a hydrogen atmosphere for 1 hour. After filtering off
 insoluble material using Celite, the filtrate was
 concentrated; the thus obtained residue was subjected to
 silica gel column chromatography (developing solvent:
 25 chloroform:methanol:concentrated aqueous ammonia =
 100:10:1), giving the titled compound (494 mg, 89%).

EI-MS: 578(M⁺)

¹H-NMR(CDCl₃): (two rotamers) δ 0.62(d, 21/10H, J=6.9Hz),

0.75(d,9/10H,J=6.6Hz), 0.84(d,9/10H,J=6.6Hz),
0.93(d,21/10H,J=6.3Hz), 1.36(s,27/10H), 1.39(s,63/10H),
2.20-2.45(m,1H), 2.46-2.95(m,8H), 3.02-3.17(m,3H), 3.61-
4.05(m,2H), 4.18-4.37(m,1H), 4.87-4.95(m,7/10H), 5.23-
5 5.35(m,3/10H), 5.55-5.70(m,3/10H), 6.20-6.50(m,7/10H),
6.60-7.20(m,7H), 8.01(d,1H,J=7.6Hz)

Example 15

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-
10 methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-
carbamidomethylethylamide

(1) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-
hydroxymethylethyl carbamic acid benzyl ester

To a solution of Z-Phe(3-tBu-4-benzyloxy)-OMe (2.46 g,
15 5.19 mmol) in THF (50 ml), lithium borohydride (339 mg,
15.57 mmol) was added under cooling with ice and stirred at
room temperature for 3 hours. The reaction mixture was
mixed with a saturated aqueous ammonium chloride solution
and extracted with ethyl acetate. The organic layer was
20 washed with saturated brine, dried over anhydrous magnesium
sulfate and evaporated to remove the solvent under reduced
pressure; the thus obtained residue was subjected to silica
gel column chromatography (developing solvent: n-
hexane:ethyl acetate = 2:1), giving the titled compound
25 (2.30 g, 99%).

¹H-NMR(CDCl₃):δ 1.38(9H,s), 2.11(1H,brs),
2.80(2H,d,J=6.9Hz), 3.54-3.77(2H,m), 3.83-3.97(1H,m), 4.88-
4.97(1H,m), 5.09(4H,s), 6.85(1H,d,J=8.3Hz),

6.97(1H,dd,J=8.3,1.8Hz), 7.11(1H,d,J=1.8Hz), 7.27-
7.50(10H,m)

(2) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonyloxymethylethylcarbamic acid benzyl ester

5 To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-hydroxymethylethylcarbamic acid benzyl ester (1.87 g, 4.18 mmol) in pyridine (42 ml), methanesulfonyl chloride (0.36 ml, 4.60 mmol) was added under cooling with ice. After stirring for 1 hour, the mixture was mixed with water and
10 extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving the titled compound (1.93 g, 88%).

¹H-NMR(CDCl₃):δ 1.38(9H,s), 2.76-2.92(2H,m), 2.96(3H,s),
15 4.10-4.21(2H,m), 4.21-4.32(1H,m), 4.88-5.00(1H,m), 5.09(4H,s), 6.86(1H,d,J=8.6Hz), 6.98(1H,brd,J=7.9Hz), 7.11(1H,brs), 7.30-7.48(10H,m)

(3) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-cyanomethylethylcarbamic acid benzyl ester

20 To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonyloxymethylethylcarbamic acid benzyl ester 1.93 g, 4.23 mmol) in DMSO (11 ml), potassium cyanide (827 mg, 12.7 mmol) was added and heated at 70°C. After stirring for 4 hours, the mixture was mixed with water and extracted
25 with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel

column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (1.42 g, 74%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 1.38(9H,s), 2.46(1H,dd,J=16.8,4.0Hz),
2.74(1H,dd,J=16.8,4.6Hz), 2.82(1H,dd,J=13.8,8.4Hz),
5 2.96(1H,dd,J=13.8,6.5Hz), 4.07-4.18(1H,m), 4.89-4.98(1H,m),
5.09(4H,s), 6.87(1H,d,J=8.3Hz), 6.99(1H,dd,J=8.3,1.5Hz),
7.12(1H,d,J=1.5Hz), 7.36-7.47(10H,m)

(4) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamine

10 To a solution of 2-(4-benzyloxy-3-tbutylphenyl)-1-cyanomethylethylcarbamic acid benzyl ester (1.38 g, 3.03 mmol) in DMSO (24 ml), potassium carbonate (1.59 g) and 30% hydrogen peroxide (4.0 ml) were added under cooling with ice. After stirring at room temperature for 2 hours, the
15 reaction mixture was mixed with water; the thus formed precipitates were collected by filtration to give 2-(4-benzyloxy-3-t-butylphenyl)-1-carbamidemethylethylcarbamic acid benzyl ester.

A mixture of the above crude compound, 20% palladium
20 hydroxide/carbon (0.50 g) and methanol (30 ml) was stirred at room temperature in a hydrogen atmosphere for 8 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography
25 (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (639 mg, 84%).

$^1\text{H-NMR}(\text{DMSO}): \delta$ 1.33(9H,s), 1.96(1H,dd,J=14.5,8.6Hz),
2.12(1H,dd,J=14.5,4.0Hz), 2.37(1H,dd,J=13.4,7.4Hz),

2.46-2.55(1H,m), 3.07-3.20(1H,m), 6.68(1H,d,J=8.2Hz),
6.73(1H,brs), 6.79(1H,brd,J=8.2Hz), 7.40(1H,brs),
9.05(1H,s)

(5) Synthesis of 2-(benzyloxycarbonyl)methylamino-3-
5 methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-
carbamidomethylethylamide

To a solution of Z-N-Me-Val-OH (736 mg, 2.78 mmol),
2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamine
(579 mg, 2.32 mmol) and CMPI (710 mg, 2.78 mmol) in THF (23
10 ml), TEA (0.77 ml) was added under cooling with ice and
stirred at room temperature for 4 hours. The reaction
mixture was mixed with water and extracted with ethyl
acetate. The organic layer was washed with saturated brine,
dried over anhydrous magnesium sulfate and evaporated to
15 remove the solvent under reduced pressure; the thus
obtained residue was subjected to silica gel column
chromatography (developing solvent: ethyl acetate), giving
the titled compound (1.09 g, 95%).

¹H-NMR(CDCl₃):δ 0.78-0.90(6H,m), 1.37(9H,s), 2.14-
20 2.80(5H,m), 2.72(3H,s), 3.92-4.04(1H,m), 4.32-4.48(1H,m),
5.04,5.15(2H,brs), 5.27-5.37(1H,m), 5.78,6.03(1H,brs),
6.38-6.82(3H,m), 7.04(1H,brs), 7.30-7.41(5H,m).

(6) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-
t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

25 To a solution of 2-(benzyloxycarbonyl)methylamino-3-
methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-
carbamidomethylethylamide (1.04 g, 2.09 mmol) in methanol
(20 ml), 10% palladium carbon (100 mg) was added and

stirred in a hydrogen atmosphere at room temperature for 1 hour. After filtration, the filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.67 g, 88%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 0.68(3H,d,J=6.9Hz), 0.83(3H,d,J=6.9Hz), 1.38(9H,s), 1.82-1.97(1H,m), 2.27(3H,s), 2.45(1H,dd,J=15.8,7.3Hz), 2.68(1H,d,J=4.6Hz), 2.78-2.91(2H,m), 4.41-4.56(1H,m), 5.30(1H,brs), 5.58(1H,brs), 6.34(1H,brs), 6.62(1H,d,J=8.0Hz), 6.92(1H,dd,J=8.0,2.0Hz), 7.04(1H,d,J=2.0Hz), 7.63(1H,brd,J=8.9Hz)

(7) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide

To a solution of Z-Phe(4-F)-OH (650 mg, 2.05 mmol), 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide (0.62 g, 1.71 mmol) and CMPI (524 mg, 2.05 mmol) in THF (17 ml), TEA (0.57 ml, 4.10 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate), giving 2-((2-benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)-

N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-carbamidomethylethylamide (1.05 g, 93%).

A mixture of the above compound (1.16 g, 1.75 mmol) and 10% palladium carbon (120 mg) in methanol (18 ml) was stirred at room temperature in a hydrogen atmosphere for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (761 mg, 82%).

EI-MS: 528(M⁺)

¹H-NMR(CDCl₃): δ 0.67, 0.80, 0.90, 0.92(6H, d, J=6.3-6.9Hz), 1.37, 1.39(9H, s), 2.21-3.22(6H, m), 2.61, 2.89(3H, s), 3.59-3.88, 4.34-4.48(3H, m), 5.33, 5.42(1H, brs), 5.90, 6.07(1H, brs), 6.56-7.18(7H, m), 8.71(1H, brd, J=8.3Hz)

Example 16

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamide

(1) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-toluenesulfonyloxymethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-hydroxymethylethylcarbamic acid benzyl ester (2.07 g, 4.63 mmol) in pyridine (46 ml), toluenesulfonyl chloride (6.79 g, 35.6 mmol) was added under cooling with ice. After stirring for 6.5 hours, the mixture was mixed with water and extracted with ethyl acetate. The organic layer was

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washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 2:1), giving the titled compound (2.46 g, 88%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 1.36(9H,s), 2.42(3H,s), 2.72-2.86(2H,m), 3.92-4.09(3H,m), 4.84-4.95(1H,m), 5.04(2H,s), 5.07(2H,s), 6.79(1H,d,J=8.0Hz), 6.87(1H,brd,J=8.0Hz), 7.06(1H,brs), 7.26-7.48(12H,m), 7.76(2H,d,J=8.3Hz)

(2) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methylthiomethylethylcarbamic acid benzyl ester

To a solution of 2-(4-benzyloxy-3-t-butylphenyl)-1-toluenesulfonyloxymethylethylcarbamic acid benzyl ester 2.4 g, 3.99 mmol) in ethanol (40 ml), a solution of sodium methanethiolate (560 mg, 7.99 mmol) in methanol (4 ml) was added and stirred at 40°C for 3 hours. The mixture was evaporated under reduced pressure to remove the solvent, mixed with a saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 5:1), giving the titled compound (1.63 g, 86%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 1.38(9H,s), 2.12(3H,s), 2.61(2H,d,J=5.6Hz), 2.85(2H,d,J=6.3Hz), 3.99-4.12(1H,m), 4.80-4.91(1H,m),

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5.09(4H,s), 6.85(1H,d,J=8.3Hz), 6.96(1H,brd,J=7.6Hz),
7.11(1H,brs), 7.27-7.50(10H,m)

(3) Synthesis of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonylmethylethylcarbamic acid benzyl ester

5 To a solution of benzyl ester of 2-(4-benzyloxy-3-t-butylphenyl)-1-methylthiomethylethylcarbamic acid (1.54 g, 3.23 mmol) in THF (75 ml) and water (25 ml), oxone (5.91 g, 6.46 mmol) was added at room temperature. After stirring for 1 hour, the mixture was mixed with water and extracted
10 with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: n-hexane:ethyl
15 acetate = 1:1), giving the titled compound (1.59 g, 97%).

¹H-NMR(CDCl₃):δ 1.38(9H,s), 2.88(3H,brs),
3.00(2H,brd,J=6.9Hz), 3.17(1H,dd,J=14.8,4.6Hz), 4.19-
4.30(1H,m), 4.35-4.47(1H,m), 5.07-5.18(1H,m), 5.09(2H,s),
5.10(2H,s), 6.85(1H,d,J=8.5Hz), 6.97(1H,dd,J=8.5,1.7Hz),
20 7.10(1H,brs), 7.28-7.49(10H,m)

(4) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-methanesulfonylmethylethylamine

A mixture of 2-(4-benzyloxy-3-t-butylphenyl)-1-methanesulfonylmethylethylcarbamic acid benzyl ester (1.0 g, 1.96 mmol) and 20% palladium hydroxide/carbon (0.08 g) in
25 methanol (16 ml) was stirred at room temperature in a hydrogen atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced

pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.56 g, 99%).

5 $^1\text{H-NMR}(\text{CDCl}_3): \delta$ 1.40(9H,s), 2.64(1H,dd,J=13.7,7.9Hz),
2.73(1H,dd,J=13.7,5.9Hz), 2.93-3.03(1H,m), 2.98(3H,s),
3.13(1H,dd,J=14.2,2.0), 3.61-3.74(1H,m), 6.62(1H,d,J=7.9Hz),
6.88(1H,dd,J=7.9,2.0), 7.05(1H,d,J=2.0Hz)

(5) Synthesis of 2-(benzyloxycarbonyl)methylamino-3-
10 methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-
methanesulfonylmethylethylamide

To a solution of Z-N-Me-Val-OH (518 mg, 1.96 mmol),
2-(3-t-butyl-4-hydroxyphenyl)-1-
methanesulfonylmethylethylamine (0.47 g, 1.63 mmol) and
15 CMPI (500 mg, 1.96 mmol) in THF (16 ml), TEA (0.55 ml) was
added under cooling with ice and stirred at room
temperature for 2 hours. The reaction mixture was mixed
with water and extracted with ethyl acetate. The organic
layer was washed with saturated brine, dried over anhydrous
20 magnesium sulfate and evaporated to remove the solvent
under reduced pressure; the thus obtained residue was
subjected to silica gel column chromatography (developing
solvent: n-hexane:ethyl acetate = 1:1), giving the titled
compound (0.70 g, 81%).

25 $^1\text{H-NMR}(\text{CDCl}_3): \delta$ 0.83(3H,d,J=6.6Hz), 0.89(3H,d,J=6.3Hz),
1.38(9H,s), 2.14-2.33(1H,m), 2.64-2.97(2H,m), 2.74(3H,s),
2.91(3H,s), 3.13(1H,dd,J=14.6,4.6Hz),
3.29(1H,dd,J=14.6,6.9Hz), 3.94(1H,d,J=11.2Hz), 4.43-

4.57(1H,m), 4.79(1H,brs), 5.14(2H,s), 6.40-6.84(3H,m),
7.06(1H,brs), 7.37(5H,brs).

(6) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-
N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-
5 hydroxyphenyl)-1-methanesulfonylmethylethylamide

To a solution of 2-(benzyloxycarbonyl)methylamino-3-
methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-
methanesulfonylmethylethylamide (0.65 g, 1.22 mmol) in
methanol (10 ml), 10% palladium carbon (130 mg) was added
10 and stirred in a hydrogen atmosphere at room temperature
for 30 min. After filtration, the filtrate was
concentrated under reduced pressure. To a solution of the
thus obtained residue, Z-Phe(4-F)-OH (465 mg, 1.47 mmol)
and CMPI (375 mg, 1.47 mmol) in THF (15 ml), TEA (0.41 ml,
15 2.93 mmol) was added under cooling with ice and stirred at
room temperature overnight. The reaction mixture was mixed
with water and extracted with ethyl acetate. The organic
layer was washed with saturated brine, dried over anhydrous
magnesium sulfate and evaporated to remove the solvent
20 under reduced pressure; the thus obtained residue was
subjected to silica gel column chromatography (developing
solvent:n-hexane: ethyl acetate =1:1) to give 2-((2-
benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-
methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-
25 hydroxyphenyl)-1-methanesulfonylmethylethylamide (484 mg,
57%). A mixture of the above compound (424 mg, 0.609 mmol)
and 10% palladium carbon (43 mg) in methanol (16 ml) was
stirred at room temperature in a hydrogen atmosphere for 2

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hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol=15:1),

5 giving the titled compound (239 mg, 70%).

EI-MS:563(M⁺)

¹H-NMR(CDCl₃):δ 0.65,0.78,0.91,0.93(6H,d,J=6.6-7.3Hz), 1.38, 1.39(9H,s), 2.22-2.40(1H,m), 2.46-3.40(6H,m), 2.66(3H,s), 2.93(3H,s), 3.60-3.83(1H,m), 3.87,4.26(1H,d,J=10.8Hz),
10 4.38-4.67(1H,m), 6.57-7.17,8.88(8H,m)

Example 17

Synthesis of 2-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-
15 butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

(1) Synthesis of 3-tBu-tyrosinol

To a solution of Z-3-tBu-tyrosinol (8.2 g, 23 mmol) in methanol (250 ml), 10% palladium carbon (800 mg) was added and stirred in a hydrogen atmosphere at room
20 temperature for 10 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the titled compound (5.1 g, 99%).

¹H-NMR(CDCl₃):δ 1.40(9H,s), 2.45(1H,dd,J=8.6,13.5Hz), 2.71(1H,dd,5.3,13.5Hz), 3.0-3.2(1H,m),
25 3.38(1H,dd,J=7.6,10.5Hz), 3.65(1H,dd,J=3.6,10.5Hz), 6.61(1H,d,J=7.9Hz), 6.88(1H,dd,J=2.0,7.9Hz), 7.06(1H,d,J=2.0Hz)

(2) Synthesis of (2-(benzyloxycarbonyl-N-methylamino)-3-

methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

To a solution of 3-tBu-tyrosinol (1 g, 4.48 mmol), Z-N-Me-Val-OH (1.43 g, 5.4 mmol) and CMPI (1.38 g, 5.4 mmol) in THF (45 ml), TEA (2.2 ml, 15.8 mmol) was added under
5 cooling with ice and stirred at room temperature for 13 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced
10 pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 1:1), giving the titled compound (1.9 g, 90%).

¹H-NMR(CDCl₃):δ 0.84(3H,d,J=6.6Hz), 0.92(3H,d,J=6.3Hz),
2.1-2.3(1H,m), 2.5-2.8(5H,m), 3.5-3.7(2H,m), 3.9-4.2(2H,m),
15 5.13(2H,s), 6.2-6.4(1H,m), 6.45(1H,d,J=7.6Hz),
6.80(1H,brd,J=7.6Hz), 7.05(1H,brs), 7.36(5H,s)

(3) Synthesis of 2-(2-((2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

20 To a solution of (2-(benzyloxycarbonyl-N-methylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (1.9 g, 4 mmol) in methanol (40 ml), 10% palladium carbon (190 mg) was added and stirred in a hydrogen atmosphere at room temperature for 3 hours. The
25 reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-(N-methylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (1.4 g).

5 To a solution of the above crude compound (1.4 g),
Boc-Phe(4-F)-OH (1.4 g, 4.94 mmol) and CMPI (1.3 g, 5.09
mmol) in THF (40 ml), TEA (2 ml, 14.3 mmol) was added under
cooling with ice and stirred at room temperature for 12
hours. The reaction mixture was mixed with water and
extracted with ethyl acetate. The organic layer was washed
with saturated brine, dried over sodium sulfate and
evaporated to remove the solvent under reduced pressure;
the thus obtained residue was subjected to silica gel
10 column chromatography (developing solvent: hexane:ethyl
acetate = 1:1), giving the titled compound (1.9 g, 78%).

¹H-NMR(CDCl₃):δ 0.77, 0.92, and 1.02(total 6H,d), 1.2-
1.5(18H,m), 2.2-3.1(8H,m), 3.5-3.8(2H,m), 4.0-4.3, 4.4-4.5,
4.7-4.9, and 5.2-5.4(total 2H,m), 6.3-7.5(8H,m)

15 (4) Synthesis of 2-(2-((2-amino-3-(4-
fluorophenyl)propionyl)-N-methylamino)-3-methyl-
butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol

To a solution of 2-(2-((2-(t-butoxycarbonylamino)-3-
(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-
20 butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propanol (0.5 g) in
methylene chloride (2 ml), TFA (2 ml) was added under
cooling with ice, stirred for 1 hour at room temperature
and evaporated to remove the solvent under reduced pressure.
The thus obtained residue was mixed with methylene chloride,
25 washed with a saturated aqueous NaHCO₃ solution, dried over
anhydrous magnesium sulfate and evaporated to remove the
solvent under reduced pressure. The thus obtained residue
was subjected to silica gel column chromatography

(developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (250 mg, 60%).

EI-MS:501(M⁺)

¹H-NMR(CDCl₃):δ 0.68, 0.79, and 0.93(total 6H,d,J=6.3-6.9Hz), 1.36 and 1.39(total 9H,s), 2.2-2.4(1H,s), 2.5-3.2(4H,m), 2.68 and 2.84(total 3H,s), 3.5-3.9(3H,m), 3.89 and 4.43(total 1H,d,J=10.9Hz), 4.0-4.4(1H,m), 6.5-7.1(7H,m), 6.58 and 8.41(total 1H,d,J=6.9-7.6Hz)

10 Example 18

(2-(2-(2-amino-3-(4-fluorophenyl)propylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

(1) Synthesis of (2-(2-(benzyloxycarbonylamino)-3-methylbutyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

To a solution of (2-(benzyloxycarbonylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (797 mg, 1.56 mmol) in methanol (15 ml), 10% palladium hydroxide (80 mg) was added and stirred at room temperature for 12 hours in a hydrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-amino-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (400 mg, 90%).

To a solution of the above crude compound (400 mg, 1.4 mmol), Z-Val-OH (528 mg, 2.1 mmol) and CMPI (539 mg, 2.1 mmol) in THF (10 ml), TEA (0.58 ml, 4.2 mmol) was added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water and

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extracted with ethyl acetate. The organic layer was washed
with saturated brine, dried over sodium sulfate and
evaporated to remove the solvent under reduced pressure;
the thus obtained residue was subjected to silica gel
5 column chromatography (developing solvent: hexane:ethyl
acetate = 1:1), giving the titled compound (504 mg, 69%).
¹H-NMR(CDCl₃):δ 0.79(3H,d,J=6.9Hz), 0.91(3H,d,J=6.6Hz),
1.38(9H,s), 2.0-2.2(1H,m), 2.89(3H,s), 2.97(2H,d,J=6.9Hz),
3.1-3.4(2H,m), 3.94(1H,dd,J=5.6,7.9Hz), 4.4-4.6(1H,m),
10 5.10(2H,s), 5.1-5.2(1H,m), 5.35(1H,brs), 6.59(1H,d,J=8.3Hz),
6.5-6.7(1H,m), 6.88(1H,brd,J=8.3Hz), 7.05(1H,brs),
7.34(5H,s)

(2) Synthesis of of (1-formyl-2-(4-
fluorophenyl)ethyl)carbamic acid tBu ester

15 To a solution of Boc-Phe(4-F)-OH (1 g, 3.53 mmol) and
O,N-dimethylhydroxylamine hydrochloride (0.38 g, 3.9 mmol)
in methylene chloride (17 ml), TEA (1.1 ml, 7.9 mmol) and
BOP (1.64 g, 3.7 mmol) were added under cooling with ice
and stirred at room temperature for 1.5 hours. The
20 reaction mixture was mixed with water and extracted with
ethyl acetate. The organic layer was washed with saturated
brine, dried over sodium sulfate and evaporated to remove
the solvent under reduced pressure; the thus obtained
residue was subjected to silica gel column chromatography
25 (developing solvent: hexane:ethyl acetate = 1:1), giving N-
methoxy-N-methyl-2-(t-butoxycarbonylamino)-3-(4-
fluorophenyl)propylamide (1.08 g, 94%).

To a solution of the above compound (1 g, 3.07 mmol)

in ether (30 ml), lithium aluminum hydride (120 mg, 3.16 mmol) was added at -10°C and stirred at the same temperature for 10 min. The reaction mixture was mixed with 15 ml of a solution of potassium hydrogen sulfate (630 mg, 4.63 mmol). The reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: hexane:ethyl acetate = 2:1), giving the titled compound (0.8 g, 98%).

¹H-NMR(CDCl₃):δ 1.44(9H,s), 3.0-3.2(2H,m), 4.3-4.5(1H,m), 5.02(1H,brs), 7.00(2H,t,J=8.6Hz), 7.13(2H,dd,J=5.4,8.6Hz), 9.63(1H,s)

(3) Synthesis of (2-(2-(2-(t-butoxycarbonylamino)-3-(4-fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone

To a solution of (2-(2-(benzyloxycarbonylamino)-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (500 mg, 0.96 mmol) in methanol (10 ml), 10% palladium carbon (50 mg) was added and stirred in a hydrogen atmosphere at room temperature for 12 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-(2-amino-3-methyl-butyrylamino)-3-(3-tBu-4-hydroxyphenyl)propyl)methylsulfone (330 mg).

To a solution of the above crude compound (330 mg, 0.86 mmol) and (1-formyl-2-(4-fluorophenyl)ethyl)carbamic

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acid tBu ester (275 mg, 1.03 mmol) in methanol (8 ml),
acetic acid (0.07 ml, 1.22 mmol) and sodium
cyanoborohydride (85 mg, 1.29 mmol) were added in that
order under cooling with ice and stirred at room
5 temperature for 30 min. The reaction mixture was mixed
with methylene chloride, washed with a saturated aqueous
NaHCO₃ solution, dried over anhydrous magnesium sulfate and
evaporated to remove the solvent under reduced pressure.
The thus obtained residue was subjected to silica gel
10 column chromatography (developing solvent:
chloroform:methanol:aqueous ammonia = 40:1:0.1), giving the
titled compound (520 mg, 95%).

¹H-NMR(CDCl₃):δ 0.68(3H,d,J=5.6Hz), 0.85(3H,d,J=6.9Hz),
1.38(9H,s), 1.41(9H,s), 1.9-2.1(1H,m), 2.4-2.9(5H,m),
15 2.9-3.1(2H,m), 2.99(3H,s), 3.1-3.3(2H,m), 3.8-4.0(1H,m),
4.47(1H,d, J=8.9Hz), 4.5-4.8(1H,m), 5.56(1H,brs),
6.64(1H,d,J=7.9Hz), 6.9-7.2(6H,m), 7.7-7.9(1H,m)

(4) Synthesis of (2-(2-(2-amino-3-(4-
fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-tBu-
20 4-hydroxyphenyl)propyl)methylsulfone

To a solution of (2-(2-(2-(t-butoxycarbonylamino)-3-
(4-fluorophenyl)propylamino)-3-methyl-butyrylamino)-3-(3-
tBu-4-hydroxyphenyl)propyl)methylsulfone (520 mg) in
methylene chloride (2 ml), TFA (2 ml) was added under
25 cooling with ice, stirred at room temperature for 30 min.
and evaporated to remove the solvent under reduced pressure.
The thus obtained residue was mixed with methylene chloride,
washed with a saturated aqueous NaHCO₃ solution, dried over

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anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 20:1:0.1), giving the titled compound (400 mg, 91%).

EI-MS:535(M⁺)

¹H-NMR(CDCl₃):δ 0.75(3H,d,J=6.9Hz), 0.89(3H,d,J=6.9Hz), 1.39(9H,s), 2.0-2.1(1H,m), 2.3-2.5(2H,m), 2.53(1H,dd,J=3.6,11.6Hz), 2.72(1H,dd,J=4.6,13.2Hz), 2.80(1H,d,J=4.6Hz), 2.8-3.1(5H,m), 3.19(2H,d,J=5.9Hz), 4.5-4.7(1H,m), 6.62(1H,d,J=7.9Hz), 6.93(1H,dd,J=2.0,7.9Hz), 6.99(2H,t,J=8.8Hz), 7.0-7.2(3H,m), 7.80(1H,d,J=8.6Hz)

Example 19

2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone

(1) Synthesis of 3-(4-benzyloxy-3-tert-butylphenyl)-2-benzyloxycarbonylamino propionitrile

To a solution of Z-Phe(4-benzyloxy-3-tBu)-NH₂ (4.6 g, 10 mmol) in THF (20 ml), pyridine (1.6 ml, 20 mmol) and trifluoroacetic anhydride (1.55 ml, 11 mmol) were added under cooling with ice and stirred for 4.5 days at room temperature. The reaction mixture was evaporated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:4), giving the titled compound (3.35 g, 99%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 1.37(9H,s), 3.0(2H,m), 4.85(1H,brd),
5.03(1H,brd), 5.10(2H,s), 5.14(2H,s), 6.69(1H,d,J=8.58Hz),
7.05(1H,d,J=8.58Hz) 7.2(1H,s), 7.3-7.5(10H,m)

(2) Synthesis of 2-[2-(4-benzyloxy-3-tert-butylphenyl)-1-
5 benzyloxycarbonylaminoethyl]-6-methyl-4-pyrimidinone

A solution of 3-(4-benzyloxy-3-tert-butylphenyl)-2-
benzyloxycarbonylaminopropionitrile (3.48 g, 7.85 mmol) in
saturated hydrochloric acid/ethanol (50 ml) was stirred at
room temperature for 1.5 days. The reaction mixture was
10 concentrated under reduced pressure and the thus obtained
residue was dissolved in ethanol (70 ml); into the thus
obtained solution, gaseous ammonia was blown under cooling
with ice, followed by stirring at room temperature for 17
hours. The resultant was concentrated under reduced
15 pressure; the thus obtained residue was dissolved in
methanol (50 ml), mixed with methyl acetoacetate (0.640 ml)
and potassium hydroxide (562 mg) and stirred at room
temperature for 4.5 days. The mixture was mixed with a
saturated aqueous ammonium chloride solution and extracted
20 with methylene chloride. The organic layer was dried over
anhydrous magnesium sulfate, evaporated to remove the
solvent under reduced pressure; the thus obtained residue
was subjected to silica gel column chromatography
(developing solvent: n-hexane:ethyl acetate = 2:1), giving
25 the titled compound (1.76 g, 67%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 1.39(9H,s), 2.25(3H,s), 3.09(2H,brd),
4.89(1H,brd), 5.03(2H,s), 5.07(2H,s), 5.80(1H,brd),
6.14(1H,s), 6.79(1H,d,J=8.24Hz), 6.92(1H,d,J=8.24Hz),

6.96(1H,s), 7.25-7.43(10H,m)

(3) Synthesis of 2-[1-amino-2-(3-tert-butyl-4-hydroxyphenyl)ethyl]-6-methyl-4-pyrimidinone

A suspension of 2-[2-(4-benzyloxy-3-tert-butylphenyl)-1-benzyloxycarbonylaminoethyl]-6-methyl-4-pyrimidinone (1.76 g, 3.35 mmol) and 20% palladium hydroxide/carbon (0.15 g) in methanol (30 ml) was stirred in a hydrogen atmosphere for 16 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving the titled compound (824 mg, 82%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 1.37(9H,s), 2.32(3H,s), 2.74(1H,dd,J=8.90,9.24Hz), 3.15(1H,dd,J=4.28,4.29Hz), 4.09(1H,m), 6.16(1H,s), 6.59(1H,d,J=7.92Hz), 6.83(1H,d,J=7.92Hz), 6.99(1H,s).

(4) Synthesis of 2-(1-(2-(benzyloxycarbonylmethylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone

To a solution of Z-N-Me-Val-OH (678 mg, 2.55 mmol), 2-[1-amino-2-(3-tert-butyl-4-hydroxyphenyl)ethyl]-6-methyl-4-pyrimidinone (700 mg, 2.32 mmol) and CMPI (653 mg, 2.55 mmol) in THF (20 ml), TEA (0.97 ml) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove

the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (0.77 g, 61%).

5 $^1\text{H-NMR}(\text{CDCl}_3): \delta$ 0.79-0.90(6H,m), 1.30(9H,m), 2.2(4H,m), 2.8-3.1(5H,m), 4.3(1H,d,J=7.3), 4.97(1H,m), 5.1-5.25(2H,m), 6.18(1H,d,J=8.58), 6.41(1H,d,J=8.58Hz), 6.5-6.85(2H,m), 7.3(5H,m)

(5) Synthesis of 2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone

A mixture of 2-(1-(2-(benzyloxycarbonylmethylamino)-3-methyl-butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (0.71 g, 1.294 mmol), 20% palladium hydroxide/carbon (0.15 g) and methanol (20 ml) was stirred in a hydrogen atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving two diastereoisomers A and B of the titled compound, A (296 mg, 38%) being eluted first and then B (77 mg, 9.4%).

(A)

25 $^1\text{H-NMR}(\text{CDCl}_3): \delta$ 0.72(3H,d,J=6.93Hz), 0.83(3H,d,J=6.93Hz), 1.34(9H,s), 1.94(1H,m), 2.28(3H,s), 2.30(3H,s), 2.77(1H,d,J=4.62Hz), 3.11(2H,m), 5.04(1H,d,J=7.59Hz), 6.14(1H,s), 6.61(1H,d,J=7.92Hz), 6.81(1H,dd,J=7.92Hz), 6.99(1H,s), 7.84(1H,d,J=6.92Hz)

(B)

¹H-NMR(CDCl₃): δ 0.84(3H,d,J=6.93Hz), 0.89(3H,d,J=6.93Hz),
1.33(9H,s), 2.00(1H,m), 2.14(3H,s), 2.18(3H,s),
2.78(1H,d,J=4.95Hz), 3.11(2H,m), 5.10(1H,d,J=6.60Hz),
5 6.14(1H,s), 6.63(1H,d,J=7.92Hz), 6.75(1H,dd,J=7.92Hz),
6.97(1H,s), 7.81(1H,d,J=7.26Hz)

(6) Synthesis of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (A)

To a solution of Boc-Phe(4-F)-OH (200 mg, 0.707 mmol),
2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone (A)
(244 mg, 0.589 mmol) and CMPI (180 mg, 0.706 mmol) in THF
15 (8 ml), TEA (0.25 ml, 4.7 mmol) was added under cooling
with ice and stirred at room temperature overnight. The
reaction mixture was mixed with water and extracted with
ethyl acetate. The organic layer was washed with saturated
brine, dried over anhydrous magnesium sulfate and
20 evaporated to remove the solvent under reduced pressure;
the thus obtained residue was subjected to silica gel
column chromatography (developing solvent: acetone:n-hexane
= 1:2), giving the titled compound (0.33 g, 82%).

¹H-NMR(CDCl₃): (two rotamers) δ 0.75, 0.80 and
25 0.98(6H,d,J=6.6,6.9Hz), 1.34 and 1.38(9H,s), 1.4 (9H,s),
2.10(1H,m), 2.3 and 2.4(3H,s), 2.7(3H,s), 2.85(2H,m),
3.04(2H,d,J=7.01Hz), 4.12 and 4.58(1H,d,J=9.6Hz),
4.75(1H,m), 5.05(1H,m), 4.83 and 5.2(1H,brd), 5.45 and

5.6(1H,dd,J=7.4Hz), 6.2(1H,s), 6.6(1H,m), 6.77(1H,m),
7.0(5H,m).

(7) Synthesis of 2-(1-(2-((2-butoxycarbonylamino-3-(4-
fluorophenyl)propionyl)-N-methylamino)-3-methyl-
5 butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-
methyl-4-pyrimidinone (B)

To a solution of Boc-Phe(4-F)-OH (63 mg, 0.222 mmol),
2-[2-(3-tert-butyl-4-hydroxyphenyl)-1-(3-methyl-2-
methylaminobutyrylamino)ethyl]-6-methyl-4-pyrimidinone (B)
10 (77 mg, 0.185 mmol) and CMPI (57 mg, 0.222 mmol) in THF (5
ml), TEA (0.08 ml, 0.573 mmol) was added under cooling with
ice and stirred at room temperature overnight. The
reaction mixture was mixed with water and extracted with
ethyl acetate. The organic layer was washed with saturated
15 brine, dried over anhydrous magnesium sulfate and
evaporated to remove the solvent under reduced pressure;
the thus obtained residue was subjected to silica gel
column chromatography (developing solvent: acetone:n-hexane
= 1:2), giving the titled compound (0.098 g, 74%).

20 ¹H-NMR(CDCl₃):(two rotamers)δ 0.78(6H,brd), 1.3-1.4(18H,s),
1.8(2H,brd), 2.25(3H,brd), 2.8 and 3.20(7H,brd), 4.1(2H,m),
4.4 and 4.5(1H,d,J=9.89Hz), 4.7 and 5.17(1H,brd), 5.3 and
5.58(1H,d,J=9.89Hz), 6.0 and 6.17(1H,s), 6.6(1H,brd), 6.7-
7.2(8H,m)

25 (8) Synthesis of 2-(1-(2-((2-amino-3-(4-
fluorophenyl)propionyl)-N-methylamino)-3-methyl-
butyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-
methyl-4-pyrimidinone (A)

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To a solution of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (A) (279 mg) in methylene chloride (8 ml), TFA (1.3 ml) was added under cooling with ice. The resultant mixture was stirred at room temperature for 1 hour and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (225 mg, 95%).

¹H-NMR(CDCl₃):(two rotamers)δ 0.7 and 0.8(6H,dd,J=6.6 and 6.59Hz), 1.29(9H,s), 2.14 and 2.275(3H,s), 2.1-2.2(1H,m), 2.67 and 2.78(3H,s), 2.6-2.8(2H,m), 3.07(2H,m), 3.7-3.83(1H,m), 4.15 and 4.62(1H,d,J=9.87Hz), 4.98 and 5.18(1H,dd,J=6.5 and 7.6Hz), 6.02 and 6.11(1H,s), 6.55 and 6.8(2H,m), 6.92(1H,d,J=6.92Hz), 6.93-7.15(4H,m)

(9) Synthesis of 2-(1-(2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (B)

To a solution of 2-(1-(2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-6-methyl-4-pyrimidinone (B) (93 mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The resultant mixture was stirred at room temperature for 1.5 hours and evaporated under reduced pressure to remove the

solvent; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (70 mg, 91.8%).

5 $^1\text{H-NMR}(\text{CDCl}_3)$: (two rotamers) δ 0.68, 0.78 and 0.86(6H, dd, $J=6.6$ and 6.27Hz), 1.3 and 1.32(9H, s), 2.21 and 2.23(3H, s), 2.2-2.4(1H, brd), 2.6 and 2.8(1H, m), 2.71-2.91(3H, s), 3.00(3H, m), 3.77 and 3.9(1H, m), 3.97 and 4.52(1H, d, $J=9.37\text{Hz}$), 4.97 and 5.18(1H, m),
10 6.12(1H, d, $J=3.3\text{Hz}$), 6.5-7.2(8H, m)

Example 20

5-(1-(2-(2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxylphenyl)ethyl)imidazolidine-2,4-dione
15

(1) Synthesis of Z-Tyr(3-tBu)-H

To a solution of Z-Tyr(3-tBu)-OMe (3.30 g, 8.57 mmol) in THF (200 ml), diisobutyl aluminum hydride (1.0 M toluene solution) (42.9 ml, 42.9 mmol) was added dropwise at -78°C
20 over 15 min. After stirring for 1 hour, the mixture was mixed with methanol and a saturated aqueous NaHCO_3 solution and extracted with ethyl acetate. The organic layer was washed with water and then with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the
25 solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (2.18 g, 72%).

NMR(CDCl₃):δ 1.37(9H,s), 3.00-3.14(2H,m), 4.40-4.52(1H,m),
4.89(1H,brs), 5.12(2H,s), 5.22-5.32(1H,m),
6.57(1H,d,J=8.2Hz), 6.82(1H,d,J=8.2Hz), 7.00(1H,s), 7.30-
7.42(5H,m), 9.64(1H,s)

5 (2) Synthesis of 5-(1-(benzyloxycarbonylamino)-2-(3-tert-
butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione

To a solution of Z-Tyr(3-tBu)-H (2.18 g, 6.14 mmol)
in ethanol (25 ml), potassium cyanide (480 mg, 7.37 mmol),
30% ammonium carbonate (1.77 g, 18.4 mmol) and water (25
10 ml) were added and stirred at 60°C for 8 hours. The mixture
was left for cooling and mixed with a saturated aqueous
NaHCO₃ solution. The organic layer was extracted with ethyl
acetate and washed with water and then with saturated brine,
dried over anhydrous magnesium sulfate and evaporated to
15 remove the solvent under reduced pressure; the thus
obtained residue was subjected to silica gel column
chromatography (developing solvent: ethyl acetate:n-hexane
= 1:1), giving the titled compound (1.38 g, 53%).

¹H-NMR(CDCl₃):δ 1.37(9H,s), 2.90-3.00(2H,m), 3.10-
20 3.22(1H,m), 4.27(1H,brs), 5.06(2H,s), 5.02-5.12(1H,m),
6.07(1H,brs), 6.57(1H,d,J=8.2Hz), 6.88(1H,dd,J=2.0,8.2Hz),
7.10(1H,d,J=2.0Hz), 7.22-7.40(5H,m)

(3) Synthesis of 5-(1-(2-(benzyloxycarbonyl-N-
methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-
25 hydroxyphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(benzyloxycarbonylamino)-2-(3-
tert-butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione
(543 mg, 1.28 mmol) in methanol (10 ml), 10% palladium

carbon (55 mg) was added and stirred at room temperature in a hydrogen atmosphere for 3 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; to a solution of the thus obtained
 5 residue in THF (13 ml), Z-N-Me-Val-OH (509 mg, 1.92 mmol), CMPI (491 mg, 1.92 mmol) and TEA (0.535 ml, 3.84 mmol) were added under cooling with ice and stirred at room temperature for 3 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic
 10 layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1), giving the titled
 15 compound (365 mg, 53%).

¹H-NMR(CDCl₃): δ 0.79 and 0.85(6H,d,J=6.6Hz), 2.14-2.26(1H,m), 2.60(3H,s), 2.70-2.92(2H,m), 3.89(1H,d,J=10.8Hz), 4.27(1H,brs), 4.62-4.74(2H,m), 5.14(2H,s), 6.28(1H,d,J=7.9Hz), 6.56-7.10(3H,m), 7.30-
 20 7.42(5H,m)

(4) Synthesis of 5-(1-(3-methyl-2-methylaminobutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(2-(benzyloxycarbonyl-N-
 25 methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione (363 mg, 0.675 mmol) in methanol (10 ml), 10% palladium carbon (50 mg) was added and stirred at room temperature in a hydrogen

2.92(3H,s), 2.24-2.42(1H,m), 2.64-3.12(4H,m), 3.84-
4.32(2H,m), 4.50-4.82(2H,m), 5.02-5.12(2H,m), 5.20-
5.64(1H,m), 6.21(1H,brs), 6.31(1H,brs), 6.50-6.60(2H,m),
6.86-7.14(5H,m), 7.24-7.40(5H,m), 7.50-8.00(1H,m)

- 5 (6) Synthesis of 5-(1-(2-(2-amino-3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione

To a solution of 5-(1-(2-(2-(benzyloxycarbonylamino)-
10 3-(4-fluorophenyl)propanoyl)-N-methylamino)-3-methylbutyrylamino)-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)imidazolidine-2,4-dione (157 mg, 0.223 mmol) in methanol (5 ml), 10% palladium carbon (50 mg) was added and stirred at room temperature in a hydrogen
15 atmosphere overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to preparative TLC (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (83.0 mg, 65%).

- 20 FAB-MS: 570(M+H⁺)

¹H-NMR(DMSO-d₆): (two rotamers) δ 0.48-0.84(6H,m), 1.28, 1.32 and 1.33(9H,s), 2.00-2.12(1H,m), 2.28, 2.42 and 2.62(3H,s), 2.40-3.10(4H,m), 3.82-4.08(2H,m), 4.24-4.50(2H,m), 6.58-7.30(7H,m), 7.66-8.30(2H,m), 8.92-9.24(2H,m)

25

Example 21

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-

hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

(1) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylcarbamic acid benzyl ester

To a solution of Z-Tyr(3-tBu)-OMe (4.0 g, 10.39 mmol) in ethanol (100 ml), hydrazine monohydrate (6.4 ml, 103.9 mmol) was added at room temperature. The mixture was stirred overnight and evaporated under reduced pressure to remove the solvent. The thus obtained residue was mixed with ethyl orthoformate (100 ml) and p-toluenesulfonic acid monohydrate (198 mg, 1.04 mmol) at room temperature. The mixture was stirred for 1.5 hours and mixed with 1N HCl (100 ml). The mixture was stirred for 20 min., and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium bicarbonate solution and then with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.34 g, 33%).

¹H-NMR(CDCl₃): δ 1.32(9H,s), 3.19(2H,brs), 5.02(1H,brs), 5.05-5.16(2H,m), 5.35(2H,brs), 6.53(1H,d,J=7.9Hz), 6.75(1H,dd,J=7.9,2.0Hz), 6.85(1H,d,J=2.0Hz), 8.34(1H,s)

(2) Synthesis of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamine

To a solution of 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylcarbamic acid benzyl ester (1.25 g, 3.16 mmol) in methanol (30 ml), 10% palladium carbon

(130 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1 day. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.80 g, 97%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 1.36(9H,s), 3.02(1H,dd,J=13.8,7.9Hz), 3.18(1H,dd,J=13.8,5.6Hz), 4.47(1H,dd,J=7.9,5.6Hz), 6.57(1H,d,J=7.9Hz), 6.84(1H,dd,J=7.9,2.0Hz), 6.97(1H,d,J=2.0Hz), 8.40(1H,s)

(3) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

To a solution of Z-N-Me-Val-OH (914 mg, 3.45 mmol), 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamine (0.75 g, 2.87 mmol) and CMPI (881 mg, 3.45 mmol) in THF (30 ml), TEA (0.96 ml) was added under cooling with ice and stirred at room temperature for 2 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving 2-benzyloxycarbonylamino-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide (1.28 g, 88%).

To a solution of the above compound (1.23 g) in

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methanol (24 ml), 10% palladium carbon (120 mg) was added and stirred in a hydrogen atmosphere at room temperature for 1 hour. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (0.87 g, 96%).

¹H-NMR(CDCl₃):δ 0.70(3H,d,J=6.9Hz), 0.85(3H,d,J=6.9Hz), 1.35(9H,s), 1.88-2.03(1H,m), 2.34(3H,s), 2.77(1H,d,J=4.6Hz), 3.12(1H,dd,J=14.0,8.4Hz), 3.28(1H,dd,J=14.0,5.9Hz), 5.45(1H,brs), 5.61-5.71(1H,m), 6.58(1H,d,J=8.0Hz), 6.68(1H,dd,J=8.0,2.0Hz), 6.96(1H,d,J=2.0Hz), 7.84(1H,brd,J=8.9Hz), 8.35(1H,s)

(4) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide

To a solution of Z-Phe(4-F)-OH (835 mg, 2.63 mmol), 3-methyl-2-methylaminobutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-oxadiazol-2-yl)ethylamide (0.82 g, 2.19 mmol) and CMPI (672 mg, 2.63 mmol) in THF (22 ml), TEA (0.74 ml, 5.26 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column

chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving 2-(2-benzyloxycarbonylamino-3-(4-fluorophenyl)propionyl)amino-N,3-dimethylbutyric acid 1-(1,3,4-oxadiazol-2-yl)-2-(3-t-butyl-4-hydroxyphenyl)ethylamide (1.31 g, 89%).

A mixture of the above compound (1.31 g, 1.95 mmol) and 10% palladium carbon (130 mg) in methanol (20 ml) was stirred at room temperature in a hydrogen atmosphere for 4 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (752 mg, 72%).

EI-MS:539(M⁺)

¹H-NMR(CDCl₃):(two rotamer)δ 0.75, 0.78, 0.89, 0.92(6H,d,J=6.3-6.6Hz), 1.29,1.34(9H,s), 2.24-2.45(1H,m), 2.50-2.85(2H,m), 2.82(3H,s), 3.04-3.20(3H,m), 3.52-3.60,3.72-3.85(1H,m), 3.99,4.43(1H,d,J=10.9Hz), 5.42-5.53,5.64-5.73(1H,m), 6.42-7.18(7H,m), 8.33,8.42(1H,s), 9.62(1H,brd,J=9.2Hz)

Example 22

2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide

(1) Synthesis of N-Me-Val-Tyr(3-tBu)-NH₂

To a solution of Tyr(3-tBu)-OCH₃ (1.5 g, 5.97 mmol) in MeOH (10 ml), aqueous ammonia (10 ml) was added and

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stirred at room temperature overnight. The mixture was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving Tyr(3-tBu)-NH₂ (1.4 g, 99%).

To a solution of the thus obtained Tyr(3-tBu)-NH₂ (1 g, 4.23 mmol), Z-N-Me-Val-OH (1.23 g, 4.63 mmol) and CMPI (1.2 g, 4.69 mmol) in THF (20 ml), TEA (1.8 ml) was added under cooling with ice and stirred at room temperature for 4 hours. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 2:1), giving Z-N-Me-Val-Tyr(3-tBu)-NH₂ (1.7 g, 83%).

A mixture of the thus obtained Z-N-Me-Val-Tyr(3-tBu)-NH₂ (1.7 g), 20% palladium hydroxide/carbon (0.15 g) and methanol (30 ml) was stirred at room temperature in a hydrogen atmosphere for 1 hour. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 10:1), giving the titled compound (1.07 g, 88%).

¹H-NMR(CDCl₃): δ 0.67(3H, d, J=6.27Hz), 0.80(3H, d, J=6.6Hz),

1.35(9H,s), 1.91(1H,m), 2.25(3H,s), 2.76(1H,d,J=4.62Hz),
3.00(2H,m), 4.75(1H,q,J=6.6Hz), 6.13(1H,s), 6.55(1H,s),
6.66(1H,d,J=7.92Hz), 6.89(1H,d,J=7.59Hz), 7.02(1H,s),
7.84(1H,d,J=7.91Hz)

5 (2) Synthesis of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH₂

To a solution of Boc-Phe(4-F)-OH (890 mg, 3.14 mmol),
N-Me-Val-Tyr(3-tBu)-NH₂ (1 g, 2.86 mmol) and CMPI (804 mg,
3.15 mmol) in THF (20 ml), TEA (1.2 ml, 7.16 mmol) was
added under cooling with ice and stirred at room

10 temperature overnight. The reaction mixture was mixed with
water and extracted with ethyl acetate. The organic layer
was washed with saturated brine, dried over anhydrous
magnesium sulfate and evaporated to remove the solvent
under reduced pressure; the thus obtained residue was
15 subjected to silica gel column chromatography (developing
solvent: acetone:n-hexane = 1:2), giving Boc-Phe(4-F)-N-Me-
Val-Tyr(3-tBu)-NH₂ (1.5 g, 85%).

(3) Synthesis of 2-((2-tertbutoxycarbonylamino-3-(4-
fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid
20 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-
yl)ethylamide

A solution of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH₂
(600 mg, 0.976 mmol) and N,N-dimethylacetamide (0.2 ml, 1.5
mmol) in dioxane (3 ml) was stirred at room temperature for
25 1 hour and mixed with a solution of sodium hydroxide (108
mg) and hydroxylamine hydrochloride (190 mg) in acetic
acid/water (7 ml/3 ml). The mixture was stirred at room
temperature for 10 min., mixed with water and filtered; a

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10 solution of the thus obtained precipitate in acetic
acid/dioxane (10 ml/10 ml) was stirred at 60°C overnight.
The reaction mixture was mixed with water and extracted
with ethyl acetate. The organic layer was washed with
5 saturated brine, dried over anhydrous magnesium sulfate and
evaporated to remove the solvent under reduced pressure;
the thus obtained residue was subjected to silica gel
column chromatography (developing solvent: ethyl acetate:n-
hexane = 1:1), giving the titled compound (474 mg, 76%).
10 ¹H-NMR(CDCl₃):(two rotamers)δ 0.76, 0.8, 0.86 and
0.98(6H,d,J=6.59,6.93,6.27,and 6.26Hz), 1.28 and 1.32(9H,s),
1.25 and 1.37(9H,s), 2.15(1H,m), 2.35 and 2.92(3H,s),
2.9(3H,m), 3.15(1H,d,J=6.93Hz), 4.12 and
4.49(1H,d,J=6.92Hz), 4.8(1H,m), 5.38 and 5.5(2H,m),
15 6.65(1H,brd), 6.9-7.2 (7H,m), 8.37(1H,brd)

(4) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-
N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-
hydroxyphenyl)-1-(1,2,4-oxadiazol-5-yl)ethylamide

To a solution of 2-((2-tertbutoxycarbonylamino-3-(4-
20 fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid
2-(3-t-butyl-4-hydroxyphenyl)-1-(1,2,4-oxadiazol-5-
yl)ethylamide (440 mg) in methylene chloride (5 ml), TFA (1
ml) was added under cooling with ice. The mixture was
stirred at room temperature for 1 hour and evaporated to
25 remove the solvent under reduced pressure; the thus
obtained residue was subjected to silica gel column
chromatography (developing solvent: methylene
chloride:methanol = 15:1), giving the titled compound (370

mg, 99%).

¹H-NMR(CDCl₃):(two rotamers)δ 0.75 and 0.87 (total 6H,d and dd,J=6.59 and 6.92Hz), 1.27(9H,s), 2.17(1H,m), 2.77(2H,m), 2.83(3H,s), 3.1(2H,m), 3.55(1H,m), 3.96(1H,d,J=10.89Hz),
5 5.7(1H,m), 6.45(1H,s), 6.59(1H,d, J=5.94Hz), 6.9(1H.brd),
8.35(1H,s), 9.5(1H,d,J=8.91Hz), 6.95(2H,t,J=8.25Hz),
7.06(2H,t,J=8.25Hz)

Example 23

10 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(1) Synthesis of N-benzyloxycarbonyl-3-tBu tyrosinylthioamide

15 To a solution of Z-Tyr(3-tBu)-NH₂ (2.08 g, 5.62 mmol) in dioxane (70 ml), Lawesson's reagent (1.36 g, 3.37 mmol) was added and stirred at 80°C for 1 hour. The reaction mixture was evaporated to remove the solvent under reduced pressure and the thus obtained residue was subjected to
20 silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:3), giving the titled compound (1.66 g, 77%).

¹H-NMR(CDCl₃):δ 1.37(9H,s), 3.01-3.14(2H,m), 4.56-4.65(1H,m), 5.08(2H,s), 6.58(1H,d,J=7.9Hz),
25 6.90(1H,dd,J=7.9,1.7Hz), 7.09(1H,d,J=1.7Hz), 7.20-7.40(5H,m)

(2) Synthesis of N-benzyloxycarbonyl-2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine

To a solution of N-benzyloxycarbonyl-3-tBu
tyrosinylthioamide (21.49 g, 55.67 mmol) in ethanol (300
ml), bromoacetaldehyde diethylacetal (43 ml, 278 mmol) was
added, stirred at 80°C for 2 hours, further mixed with
5 bromoacetaldehyde diethylacetal (43 ml, 278 mmol), stirred
at 80°C for 4 hours, further mixed with bromoacetaldehyde
diethylacetal (43 ml, 278 mmol) and stirred at 80°C for 3
hours. The mixture was evaporated to remove the solvent
under reduced pressure and the thus obtained residue was
10 subjected to silica gel column chromatography (developing
solvent: ethyl acetate:n-hexane = 1:3), giving the titled
compound (15.32 g, 67%).

¹H-NMR(CDCl₃):δ 1.29(9H,s), 3.10-3.30(2H,m), 5.10(2H,s),
5.20-5.40(1H,m), 6.51(1H,d,J=8.3Hz), 6.74-6.78(2H,m), 7.22
15 (1H,d,J=3.3Hz), 7.20-7.40(5H,brs), 7.76(1H,d,J=3.3Hz)

(3) Synthesis of 2-(3-tert-butyl-4-hydroxyphenyl)-1-
(thiazol-2-yl)ethylamine

To a solution of N-benzyloxycarbonyl-2-(3-tert-butyl-
4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine (15.28 g,
20 37.27 mmol) in methylene chloride (1.1 l), thioanisole
(8.75 ml, 74.54 mmol) was added. To the mixture, a
solution of 1.0M boron tribromide in methylene chloride
(186 ml, 186.34 mmol) was added dropwise under cooling with
ice and stirred for 1 hour. The reaction mixture was mixed
25 with water and alkalinized by 2N sodium hydroxide and
extracted with methylene chloride. The organic layer was
washed with saturated brine, dried over anhydrous magnesium
sulfate and evaporated to remove the solvent under reduced

pressure, giving the titled compound (9.46 g, 90%).

¹H-NMR(CDCl₃):δ 1.36(9H,s), 2.82-3.27(2H,m), 4.51-4.56(1H,m), 6.57(1H,d,J=7.9Hz), 6.89(1H,dd,J=7.9,2.0Hz), 6.99(1H,d,J=2.0Hz), 7.27(1H,d,J=3.3Hz), 7.76(1H,d,J=3.3Hz)

5 (4) Synthesis of 2-(N-tert-butoxycarbonyl-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine (4.67 g, 16.64 mmol), Boc-N-Me-Val-OH (5.0 g, 21.63 mmol) and CMPI (5.53 g, 21.63 mmol) in THF (110 ml), TEA (5.33 ml, 38.27 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (8.10 g, 100%).

¹H-NMR(CDCl₃):δ 0.75-0.97(6H,m), 1.29(6H,s), 1.31(3H,s), 1.41(3H,s), 1.48(6H,s), 2.10-2.35(1H,m), 2.71(1.5H,s), 2.73(1.5H,s), 3.10-3.30(2H,m), 3.90-4.10(1H,m), 5.50-5.70(1H,m), 6.58(1H,d,J=7.9Hz), 6.70-6.90(2H,m), 7.20(1H,d,J=3.0Hz), 7.74-7.76(1H,m)

25 (5) Synthesis of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of 2-(N-tert-butoxycarbonyl-N-

methyldamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (8.03 g, 16.42 mmol) in methylene chloride (80 ml), TFA (40 ml) was added and stirred at room temperature for 30 min. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was mixed with methylene chloride, washed with a 2N aqueous sodium hydroxide solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: acetone:hexane = 1:2), giving two diastereoisomers A and B of the titled compound, A (2.37 g, 37%) being eluted first and then B (2.17 g, 34%).

(A)

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 0.65(3H,d,J=6.9Hz), 0.82(3H,d,J=6.9Hz), 1.33(9H,s), 1.85-2.00(1H,m), 2.32(3H,s), 2.75(1H,d,J=4.6Hz), 3.09-3.37(2H,m), 5.63-5.71(1H,m), 6.61(1H,d,J=7.9Hz), 6.87-6.92(2H,m), 7.22(1H,d,J=3.0Hz), 7.77(1H,d,J=3.3Hz)

(B)

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 0.84(3H,d,J=6.9Hz), 0.92(3H,d,J=6.9Hz), 1.33(9H,s), 1.95-2.15(1H,m), 2.11(3H,s), 2.68(1H,d,J=5.0Hz), 3.12-3.39(2H,m), 5.60-5.69(1H,m), 6.59(1H,d,J=8.2Hz), 6.87(1H,dd,J=7.9,2.0Hz), 6.93(1H,d,J=2.0Hz), 7.22(1H,d,J=3.3Hz), 7.77(1H,d,J=3.3Hz)

(6) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methyldamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(A)

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (1.00 g, 2.57 mmol), Boc-Phe(4-F)-OH (947 mg, 3.34 mmol) and CMPI (853 mg, 3.34 mmol) in THF (17 ml), TEA (0.82 ml, 5.91 mmol) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:2), giving the titled compound (1.55 g, 92%).

¹H-NMR(CDCl₃):δ 0.76(3H,d,J=6.6Hz), 0.86(2H,d,J=6.6Hz), 0.97(1H,d,J=6.6Hz), 1.26(3H,s), 1.29(6H,s), 1.37(6H,s), 1.40(3H,s), 2.15-2.40(1H,m), 2.70-3.50(4H,m), 2.78(3H,s), 4.17(0.3H,d,J=10.2Hz), 4.49(0.7H,d,J=11.2Hz), 4.70-4.85(1H,m), 5.25-5.80(1H,m), 6.58(1H,d,J=7.9Hz), 6.75-7.30(6H,m), 7.21(0.7H,d,J=3.3Hz), 7.23(0.3H,d,J=3.3Hz), 7.74(0.3H,d,J=3.3Hz), 7.77(0.7H,d,J=3.3Hz)

(7) Synthesis of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(B)

To a solution of 3-methyl-2-methylaminobutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (1.00 g, 2.57 mmol), Boc-Phe(4-F)-OH (947 mg, 3.34

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mmol) and CMPI (853 mg, 3.34 mmol) in THF (17 ml), TEA
(0.82 ml, 5.91 mmol) was added under cooling with ice and
stirred at room temperature overnight. The reaction
mixture was mixed with water and extracted with ethyl
5 acetate. The organic layer was washed with saturated brine,
dried over anhydrous magnesium sulfate and evaporated to
remove the solvent under reduced pressure; the thus
obtained residue was subjected to silica gel column
chromatography (developing solvent: ethyl acetate:n-hexane
10 = 1:2), giving the titled compound (1.54 g, 92%).

¹H-NMR(CDCl₃):δ 0.57(1H,d,J=6.6Hz), 0.62(1H,d,J=6.9Hz),
0.78(4H,d,J=6.3Hz), 1.33(9H,s), 1.36(9H,s), 2.10-2.30(1H,m),
2.60-3.70(4H,m), 2.82(1.8H,s), 2.85(1.2H,s),
3.99(0.3H,d,J=10.6Hz), 4.51(0.7H,d,J=10.9Hz), 4.70-
15 4.90(1H,m), 5.20-5.60(1H,m), 6.59-7.21(7H,m),
7.20(1H,d,J=3.3Hz), 7.71(1H,d,J=3.3Hz)

(8) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-
N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-
hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

20 To a solution of 2-((2-butoxycarbonylamino-3-(4-
fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid
2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide
(A) (1.49 g, 2.28 mmol) in methylene chloride (20 ml), TFA
(10 ml) was added and stirred at room temperature for 1.5
25 hours. The reaction mixture was evaporated to remove the
solvent under reduced pressure; the thus obtained residue
was mixed with methylene chloride, washed with a 2N aqueous
sodium hydroxide solution and saturated brine, dried over

anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (430 mg).
 EI-MS:554(M⁺)
¹H-NMR(CDCl₃):δ 0.75(2.3H,d,J=6.9Hz), 0.80(0.7H,d,J=6.6Hz), 0.90-0.92(0.7H,m), 0.93(2.3H,d,J=6.6Hz), 1.24(7H,s), 1.30(2H,s), 2.25-2.65(1H,m), 2.70-3.40(4H,m), 2.79(2.4H,s),
 10 2.85(0.6H,s), 3.50-3.60(0.8H,m), 3.75-3.90(0.2H,m), 3.97(0.8H,d,J=10.9Hz), 4.51(0.2H,d,J=10.6Hz), 5.45-5.60(0.2H,m), 5.65-5.80(0.8H,m), 6.55-7.20(7H,m), 7.23(1H,d,J=3.3Hz), 7.76(1H,d,J=3.3Hz)

(9) Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 2-((2-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide
 20 (B) (1.48 g, 2.26 mmol) in methylene chloride (20 ml), TFA (10 ml) was added and stirred at room temperature for 1.5 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was mixed with methylene chloride, washed with a 2N aqueous
 25 sodium hydroxide solution and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography

(developing solvent: methanol:aqueous ammonia:methylene chloride = 3:0.1:100), giving the titled compound (587 mg).

EI-MS:554(M⁺)

¹H-NMR(CDCl₃):δ 0.72(1.5H,d,J=6.9Hz), 0.786(1.5H,d,J=6.3Hz),
 5 0.793(1.5H,d,J=6.6Hz), 0.88(1.5H,d,J=6.3Hz), 1.24(5.4H,s),
 1.33(3.6H,s), 2.15-2.40(1H,m), 2.40-3.35(4H,m),
 2.75(1.8H,s), 2.87(1.2H,s), 3.55-3.85(1H,m),
 3.86(0.6H,d,J=10.9Hz), 4.56(0.4H,d,J=10.9Hz), 5.50-
 5.65(1H,m), 6.45-7.15(7H,m), 7.17-7.20(1H,m),
 10 7.23(1H,d,J=3.3Hz), 7.76(1H,d,J=3.0Hz)

Example 24

Synthesis of 2-((2-amino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid
 15 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide

To a solution of Boc-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH₂ (400 mg, 0.651 mmol) in methylene chloride (6.5 ml), dimethylformamide dimethylacetal (0.26 ml, 1.954 mmol) was
 20 added at room temperature. The mixture was stirred for 30 min. and evaporated to remove the solvent under reduced pressure. To a solution of the thus obtained residue in dioxane (6.5 ml), acetic acid (2 ml) and hydrazine monohydrate (48 μl, 0.977 mmol) were added at room
 25 temperature. The mixture was stirred for 40 min., mixed with water and filtered to collect the precipitated solid. The thus obtained solid was subjected to silica gel column chromatography (developing solvent: ethyl acetate), giving

2-((2-t-butoxycarbonylamino-3-(4-fluorophenyl)propionyl)-N-methylamino)-3-methylbutyric acid 2-(3-t-butyl-4-hydroxyphenyl)-1-(1,3,4-triazol-2-yl)ethylamide (384 mg, 93%).

5 To a solution of the above compound (421 mg) in methylene chloride (3 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 30 min., mixed with a saturated aqueous sodium bicarbonate solution and extracted with ethyl
10 acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent:
15 chloroform:methanol:aqueous ammonia = 100:10:1), giving the titled compound (175 mg, 49%).

EI-MS:538(M⁺)

¹H-NMR(CDCl₃):δ 0.72, 0.87, 0.73-0.80(6H, d, J=6.3-6.6Hz), 1.22, 1.25(9H, s), 2.24-2.41(1H, m), 2.50-3.30(4H, m), 2.78,
20 2.87(3H, s), 3.47-3.58, 3.79-3.88(1H, m), 4.00, 4.39(1H, brd, J=10.6Hz), 5.29-5.38, 5.40-5.50(1H, m), 6.41-7.11(7H, m), 7.52, 9.33(1H, brd, J=8.3Hz), 8.02, 8.10(1H, s)

Example 25

25 2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

(1) Synthesis of 2-tert-butoxycarbonylamino-3-

methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of Boc-Val-OH (890 mg, 4.09 mmol), 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine
5 (1.03 g, 3.73 mmol) and CMPI (653 mg, 1.05 mmol) in THF (10 ml), TEA (1 ml) was added under cooling with ice and stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine,
10 dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled compound (1.88 g, 99%).

15 ¹H-NMR(CDCl₃):δ 0.79 and 0.89(6H,d,J=6.93Hz), 1.29 and 1.31(9H,s), 1.42 and 1.44(9H,s), 2.15(1H,brd), 3.23(2H,m), 3.89(1H,m), 5.0(1H,brd), 5.4(0.7H, brd), 5.57(1H,q,J=6.93 and 5.92Hz), 6.56(1H,q,J=4.62 and 4.29Hz), 6.8(3H,brd), 7.21(1H,m), 7.75(1H,t,J=2.07 and 3.3Hz)

20 (2) Synthesis of 2-amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide

To a solution of 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamine (1.7 g) in methylene chloride (14 ml), TFA (6 ml) was added under cooling with ice and
25 stirred at room temperature for 2 hours. The mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene

chloride:methanol:ethyl acetate = 20:1:2), giving two diastereoisomers A and B of the titled compound, A (700 mg) being eluted first and then B (650 mg, 99%).

(A)

5 $^1\text{H-NMR}(\text{CDCl}_3\text{-CD}_3\text{OD})$: δ 0.89(6H,brd), 1.28(9H,s), 2.15(1H,m), 3.18-3.7(3H,m), 5.48(1H,brd), 6.6(1H,brd), 6.8(2H,brd), 7.27(1H,s), 7.7(1H,s)

(B)

10 $^1\text{H-NMR}(\text{CDCl}_3\text{-CD}_3\text{OD})$: δ 0.72(6H,d,J=6.27Hz), 1.31(9H,s), 1.92(1H,brd), 3.04(2H,brd), 3.28(1H,dd,J=5.28 and 5.6Hz), 5.55(1H,m), 6.62(1H,d,J=7.92Hz), 6.86(1H,brd), 6.97(1H,s), 7.28(1H,s), 7.68(1H,d,J=2.64Hz)

(3) Synthesis of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

To a solution of 2-amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (600 mg, 1.59 mmol) and (1-formyl-2-(4-fluorophenyl)ethyl)carbamic acid tBu ester (640 mg, 2.39 mmol) in MeOH (10 ml), NaBH_3CN (200 mg, 3.1 mmol) was added under cooling with ice and stirred at room temperature for one hour. The mixture was evaporated under reduced pressure, mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over sodium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:1), giving the titled

compound (935 mg, 93%).

$^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.75 and 0.83(6H,d,J=6.93 and 6.59Hz),
1.36(9H,s), 1.42(9H,s), 2.46(2H,brd), 2.66(2H,brd),
2.73(1H,d, J=4.61Hz), 2.81(1H,d, J=7.26Hz),
5 3.20(2H,d,J=6.26Hz), 3.6(2H,m), 3.8(1H,brd), 4.7(1H,brd),
5.6(1H,q,J=6.93 and 5.94Hz), 6.61(1H,d,J=7.92Hz),
6.77(1H,s), 6.85(1H,d,J=7.92Hz), 6.9-7.21(8H,m),
7.66(1H,d,J=2.97Hz)

(4) Synthesis of 2-[2-tert-butoxycarbonylamino-3-(4-
10 fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-
butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)

To a solution of 2-amino-3-methylbutyric acid 2-(3-
tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)
(600 mg, 1.59 mmol) and 1-formyl-2-(4-
15 fluorophenyl)ethyl carbamic acid tBu ester (640 mg, 2.39
mmol) in MeOH (10 ml), NaBH_3CN (200 mg, 3.1 mmol) was added
under cooling with ice and stirred at room temperature for
one hour. The mixture was evaporated under reduced
pressure, mixed with water and extracted with ethyl acetate.
20 The organic layer was washed with saturated brine, dried
over sodium sulfate and evaporated to remove the solvent
under reduced pressure; the thus obtained residue was
subjected to silica gel column chromatography (developing
solvent: ethyl acetate:n-hexane = 1:1), giving the titled
25 compound (950 mg, 95%).

$^1\text{H-NMR}(\text{CDCl}_3)$: δ 0.83 and 0.87(6H,d,J=6.93 and 6.92Hz),
1.34(9H,s), 1.41(9H,s), 2.00(1H,brd), 2.31(2H,brd), 2.6-
2.81(3H,brd), 2.81(1H,d, J=7.26Hz), 3.20(2H,m), 3.6(2H,m),

3.8(1H,brd), 4.58(1H,brd), 4.83(1H,brd),
5.59(2H,q,J=6.93Hz), 6.60(1H,d,J=7.92Hz),
6.81(1H,d,J=7.91Hz), 6.88(1H,s), 6.9-7.21(8H,m),
7.74(1H,d,J=2.29Hz)

- 5 (5) Synthesis of 2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A)

To a solution of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (A) (300
10 mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 1 hour and evaporated under reduced pressure; the thus obtained residue was subjected to silica
15 gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (180 mg, 71%).

¹H-NMR(DMSO-d₆):δ 0.78 and 0.88(6H,d,J=3.3 and 5.6Hz),
1.28(9H,s), 1.90(1H,brd), 2.6(1H,m), 2.7-3.0(3H,brd),
20 3.1(2H,m), 3.4(1H,brd), 5.29(1H,q,J=5.93 and 8.58Hz),
6.69(1H,d,J=7.92Hz), 6.86(1H,d,J=7.59Hz), 6.95(1H,s),
7.2(4H,m), 7.62(1H,d,J=2.97Hz), 7.77(1H,d,J=3.3Hz)

- (6) Synthesis of 2-[2-amino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B)
25

To a solution of 2-[2-tert-butoxycarbonylamino-3-(4-fluorophenyl)propyl]amino-3-methylbutyric acid 2-(3-tert-butyl-4-hydroxyphenyl)-1-(thiazol-2-yl)ethylamide (B) (300

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mg) in methylene chloride (5 ml), TFA (1 ml) was added under cooling with ice. The mixture was stirred at room temperature for 1 hour and evaporated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:methanol = 15:1), giving the titled compound (193 mg, 76%).

$^1\text{H-NMR}(\text{DMSO}-d_6): \delta$ 0.61(6H,q,J=6.6 and 12.54Hz), 1.3(9H,s), 1.72(1H,s), 2.7-3.0(4H,brd), 3.16(1H,s), 3.28(1H,m), 3.5(1H,brd), 5.37(1H,m), 6.65(1H,d,J=8.25Hz), 6.85(1H,d,J=10.89Hz), 7.0(1H,s), 7.2(4H,m), 7.68(1H,d,J=2.97Hz), 7.81(1H,d,J=3.3Hz)

Example 26

15 Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

(1) Synthesis of Boc-Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

To a solution of Tyr(2-F)-OH (0.60 g, 3.01 mmol) and di-tert-butyl dicarbonate (0.69 g, 3.16 mmol) in dioxane/water (5 ml/5 ml), TEA (0.84 ml, 6.02 mmol) was added under cooling with ice and stirred for 2 hours. The reaction mixture was concentrated to approximately a half volume, mixed with a saturated aqueous NaHCO₃ solution and washed with ether. The aqueous layer was rendered acidic by the addition of 2N hydrochloric acid under cooling with ice, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure, giving crude Boc-Tyr(2-F)-OH (0.85 g).

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T02121 61206960

To a solution of the above crude Boc-Tyr(2-F)-OH (0.82 g), N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.77 g, 2.11 mmol) and CMPI (0.81 g, 3.17 mmol) in THF (5 ml), TEA (1.18 ml, 8.44 mmol) was added under cooling with ice and stirred at room temperature for 23 hours. The reaction mixture was mixed with water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:concentrated aqueous ammonia = 30:1:0.05), giving the titled compound (0.21 g, 15%).

(2) Synthesis of Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

To a solution of Boc-Tyr(2-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.21 g, 0.326 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added and stirred for 15 min. The reaction mixture was concentrated under reduced pressure, mixed with a saturated aqueous NaHCO₃ solution, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate. The resultant was evaporated to remove the solvent under reduced pressure, giving the titled compound (173 mg, 82%).

EI-MS(M⁺):544

¹H-NMR(DMSO-d₆-CDCl₃):δ 0.21(6/5H,d,J=6.3Hz), 0.59(6/5H,d,J=6.6Hz), 0.71(9/5H,d,J=6.6Hz), 0.84-0.98(9/5H,m), 1.30(27/5H,s), 1.37(18/5H,s), 2.00-2.22(1H,m), 2.10(6/5H,s), 2.3-2.8(2H,m), 2.44(9/5H,s),

2.85(9/5H,d,J=5.9Hz), 3.1-3.8(2H,m), 3.24(6/5H,d,J=5.0Hz),
3.94-4.20(1H,m), 4.51(2/5H,d,J=10.2Hz),
4.78(2/5H,dd,J=3.9,11.2Hz), 4.88(3/5H,d,J=10.2Hz),
5.41(3/5H,dd,J=3.9,10.2Hz), 6.48-7.21(7.7H,m), 7.60-
5 7.75(0.3H,m), 8.88(1H,d,J=7.3Hz), 9.47(1H,brs)

Example 27

Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

(1) Synthesis of Boc-Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

10 To a solution of Tyr(3-F)-OH (0.80 g, 4.02 mmol) and
di-tert-butyl dicarbonate (0.92 g, 4.22 mmol) in
dioxane/water (7 ml/7 ml), TEA (1.12 ml, 8.04 mmol) was
added under cooling with ice and stirred for 2.5 hours.
The reaction mixture was concentrated to approximately a
15 half volume, mixed with a saturated aqueous NaHCO₃ solution
and washed with ether. The aqueous layer was rendered
acidic by the addition of 2N hydrochloric acid under
cooling with ice, and extracted with chloroform. The
organic layer was dried over anhydrous magnesium sulfate
20 and evaporated to remove the solvent under reduced pressure,
giving crude Boc-Tyr(3-F)-OH (1.18 g).

To a solution of the above crude Boc-Tyr(3-F)-OH
(1.18 g), N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (1.10 g, 3.03 mmol)
and CMPI (1.16 g, 4.55 mmol) in THF (6 ml), TEA (1.27 ml,
25 12.1 mmol) was added under cooling with ice and stirred at
room temperature for 27 hours. The reaction mixture was
mixed with water, and extracted with ethyl acetate. The
organic layer was washed with saturated brine, dried over

anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol:concentrated aqueous ammonia = 30:1:0.05), giving the titled compound (0.19 g, 10%).

(2) Synthesis of Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

To a solution of Boc-Tyr(3-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ (0.19 g, 0.294 mmol) in methylene chloride (3 ml), TFA (1.5 ml) was added and stirred for 15 min. The reaction mixture was concentrated under reduced pressure, mixed with a saturated aqueous NaHCO₃ solution, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate. The resultant was evaporated to remove the solvent under reduced pressure, giving the titled compound (136 mg, 85%).

EI-MS(M⁺):544

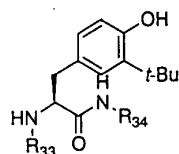
¹H-NMR (DMSO-d₆-CDCl₃):δ 0.18(6/5H,d,J=6.3Hz), 0.58(6/5H,d,J=6.6Hz), 0.68(9/5H,d,J=6.6Hz), 0.85(9/5H,d,J=6.3Hz), 1.29(27/5H,s), 1.37(18/5H,s), 1.95-2.21(1H,m), 2.04(6/5H,s), 2.30-3.00(2H,m), 2.41(9/5H,s), 2.81(9/5H,s), 3.10-3.60(16/5H,m), 3.55-6.64(3/5H,m), 4.00-4.10(2/5H,m), 4.45(2/5H,d,J=10.2Hz), 4.70(2/5H,dd,J=3.9,11.2Hz), 4.85(3/5H,d,J=10.2Hz), 5.38(3/5H,dd,J=3.9,10.2Hz), 6.51-7.31(8H,m), 8.98(1H,d,J=2.6Hz), 9.50(1H,brs)

Examples 28-64 were conducted according to Scheme 1

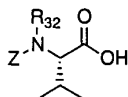
and Examples 65-78 were conducted according to Scheme 2.
 The following Reference Examples show the methods of
 preparing Intermediates of Schemes 1 and 2. Table C-1
 shows structural formulae of Intermediates of Examples 28-
 5 64.

Table C-1

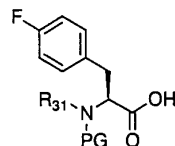
Intermediates of Examples 28-78



T 1 : R33=R34=H
 T 2 : R33=H, R34=Me
 T 4 : R33=Me, R34=H (Example 1 (5))
 T 5 : R33=R34=Me
 T 7 : R33=Et, R34=H
 T 8 : R33=Et, R34=Me
 T 1 7 : R33=Me, R34=CH₂SO₂CH₃
 T 1 8 : R33=H, R34=tBu

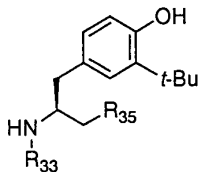


V1: R32=Me (Commercial)
 V2: R32=Et

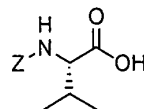


P1: PG=Boc, R31=H (Commercial)
 P2: PG=Boc, R31=Me
 P3: PG=Z, R31=Et
 P10: PG=Boc, R31=Et

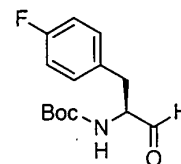
10



T19: R33=H, R35=OH (Example 17)
 T20: R33=Me, R35=H
 T21: R33=R35=H
 T22: R33=H, R35=NH(Boc) (Example 10)
 T23: R33=Me, R35=OH



V4 (Commercial)



P 1 1

In Table C-1, "(Example 1 (5))", "(Example 17)" and
 "(Example 10)" mean that the methods of preparing the
 compounds are described in the corresponding Examples 1 (5),
 15 17 and 10, respectively. "Commercial" means that the
 compound is commercially available.

Reference Example 1

Synthesis of Intermediate T1

A mixture of Tyr(3-tBu)-OMe (12.4 g, 49 mmol) and concentrated aqueous ammonia (240 ml) was stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography (CHCl₃:MeOH = 10:1), giving Tyr(3-tBu)-NH₂ (T1) (10 g, 80%).

¹H-NMR(CDCl₃): δ 1.40(9H,s), 2.63(1H,dd,J=9.6,13.9Hz), 3.19(1H,dd,J=4.0,13.9Hz), 3.58(1H,dd,J=4.0,9.6Hz), 5.11(1H,brs), 5.38(1H,brs), 6.64(1H,d,J=7.9Hz), 6.92(1H,dd,J=2.0,7.9Hz), 7.11(1H,d,J=2.0Hz).

Reference Example 2

Synthesis of Intermediate T2

A mixture of Tyr(3-tBu)-OMe (12 g, 48 mmol) and a 40% methylamine methanol solution (80 ml) was stirred at room temperature for 14 hours. The reaction mixture was concentrated under reduced pressure, giving Tyr(3-tBu)-NHMe (T2) (12 g) as a crude product.

¹H-NMR(CDCl₃): δ 1.39(9H,s), 2.60(1H,dd,J=9.6,13.9Hz), 2.83(3H,d,J=5.0Hz), 3.18(1H,dd,J=4.0,13.9Hz), 3.57(1H,dd,J=4.0,9.6Hz), 6.67(1H,d,J=7.9Hz), 6.88(1H,dd,J=1.8,7.9Hz), 7.07(1H,d,J=1.8Hz).

Reference Example 3

Synthesis of Intermediate T5

(1) Synthesis of N-formyl-Tyr(3-tBu)-OMe

To a solution of acetyl chloride (22.6 ml, 299 mmol) in diethyl ether (1 l), sodium formate (30.6 g, 450 mmol) was added under cooling with ice and stirred at room temperature for 23 hours. The reaction mixture was
 5 filtered and evaporated to remove the solvent. The thus obtained residue was added dropwise to a solution of H-Tyr(3-tBu)-OMe (22.2 g, 83.8 mmol) in methylene chloride (500 ml) under cooling with ice, mixed with TEA (46.7 ml, 335 mmol) and stirred at room temperature for 2 hours. The
 10 reaction mixture was mixed with saturated aqueous NaHCO₃ and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to
 15 silica gel column chromatography (developing solvent: n-hexane:ethyl acetate = 1:1), giving N-formyl-Tyr(3-tBu)-OMe (23.8 g, 100%).

¹H-NMR (CDCl₃): δ 1.38(9H, s), 3.09(2H, d, J=5.3Hz), 3.76(3H, s), 4.93(1H, dd, J=5.3, 13.5Hz), 5.23(1H, s), 6.02(1H, d, J=13.5Hz),
 20 6.55(1H, d, J=7.9Hz), 6.80(1H, dd, J=2.0, 7.9Hz), 6.95(1H, d, J=2.0Hz), 8.18(1H, s).

(2) Synthesis of N-Me-Tyr(3-tBu)-OMe

To a solution of N-formyl-Tyr(3-tBu)-OMe (23.8 g, 85.3 mmol) in THF (400 ml), 1.0M borane-THF complex (170
 25 ml) was added dropwise under cooling with ice over 30 min. The mixture was stirred for 20 min., mixed with methanol (50 ml) and further stirred for 30 min. The reaction mixture was mixed with 33% hydrobromic acid/acetic acid (31

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ml) and stirred for 2 hours. The mixture was neutralized by saturated aqueous NaHCO_3 under cooling with ice and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium

5 sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: chloroform:methanol=20:1), giving N-Me-Tyr(3-tBu)-OMe (20.3 g, 90%).

10 $^1\text{H-NMR}$ (CDCl_3): δ 1.38(9H,s), 2.37(3H,s), 2.89(2H,d,J=6.6Hz), 3.42(1H,t,J=6.6Hz), 3.68(3H,s), 6.55(1H,d,J=7.9Hz), 6.86(1H,dd,J=2.0,7.9Hz), 7.02(1H,d,J=2.0Hz)

(3) Synthesis of N-Me-Tyr(3-tBu)-NHMe

To a solution of N-Me-Tyr(3-tBu)-OMe (8.20 g, 31.1 mmol) in methanol (20 ml), a 30% methylamine methanol solution (200 ml) was added and stirred at room temperature for 16 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column

15 chromatography (developing solvent: chloroform:methanol=20:1), giving N-Me-Tyr(3-tBu)-NHMe (T5) (6.27 g, 76%).

20 $^1\text{H-NMR}$ (CDCl_3): δ 1.39(9H,s), 2.26(3H,s), 2.58(1H,dd,J=10.5,14.8Hz), 2.84(2H,d,J=4.9Hz), 3.06- 3.18(2H,m), 5.00(1H,brs), 6.62(1H,d,J=7.9Hz), 6.89(1H,dd,J=1.7,7.9Hz), 7.08(1H,d,J=1.7Hz), 7.15(1H,brs).

Reference Example 4

Synthesis of Intermediate T7

A mixture of Tyr(3-tBu)-NH₂ (1.6 g, 6.8 mmol) and acetaldehyde (7.6 ml, 0.14mol) was stirred under cooling with ice for 10 min. The reaction mixture was concentrated under reduced pressure under cooling with ice; the thus obtained residue was mixed with methanol (34 ml) and then under cooling with ice with sodium borohydride (0.28 g, 7.4 mmol) and stirred at the same temperature for 15 min. The resultant was mixed with water and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (CHCl₃:MeOH = 20:1), giving N-Et-Tyr(3-tBu)-NH₂ (T7) (1.3 g, 73%).

¹H-NMR(CDCl₃): δ 0.96(3H,t,J=7.3Hz), 1.40(9H,s), 2.4-2.7(3H,m), 3.14(1H,dd,J=4.0,13.9Hz), 3.26(1H,dd,J=4.0,9.6Hz), 5.25(1H,s), 5.38(1H,brs), 6.63(1H,d,J=7.9Hz), 6.91(1H,dd,J=2.0,7.9Hz), 7.10(1H,d,J=2.0Hz), 7.18(1H,brs).

20

Reference Example 5

Synthesis of Intermediate T8

A mixture of Tyr(3-tBu)-NHMe (1.7 g, 6.8 mmol), acetaldehyde (0.76 ml, 13.6 mmol) and dichloromethane (10 ml) was stirred under cooling with ice for 30 min. The reaction mixture was concentrated under reduced pressure under cooling with ice; the thus obtained residue was mixed with methanol (20 ml) and then under cooling with ice with

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sodium borohydride (0.28 g, 7.4 mmol) and stirred at the same temperature for 15 min. The resultant was mixed with water and extracted with dichloromethane. The organic layer was washed with water, dried and concentrated under reduced pressure under cooling with ice; the thus obtained residue was subjected to silica gel column chromatography (CHCl₃:MeOH=20:1), giving N-Et- Tyr(3-tBu)-NHMe (T8) (1.7 g, 90%).

¹H-NMR(CDCl₃):δ 0.94(3H,t,J=7.3Hz), 1.39(9H,s), 2.4-2.6(2H,m), 2.60(1H,dd,J=9.6,13.8Hz), 2.83(3H,d,J=4.9Hz), 3.13(1H,dd,J=4.0,13.8Hz), 3.25(1H,dd,J=4.0,9.6Hz), 5.44(1H,brs), 6.64(1H,d,J=7.9Hz), 6.88(1H,dd,J=2.0,7.9Hz), 7.07(1H,d,J=2.0Hz), 7.27(1H,brs)

15 Reference Example 6

Synthesis of Intermediate V2

To a solution of Z-Val-OH (50 g) in THF (500 ml), ethyl iodide (127.3 ml, 1592 mmol) was added under cooling with ice and then sodium hydride (60% in oil) (23.88 g, 597 mmol) was added slowly, followed by stirring at 60°C for 12 hours. The reaction mixture was mixed with water and washed with ether. The thus obtained aqueous layer was rendered acidic by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The resultant was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (H:EA:AcOH = 100:50:1),

THF/DMF (73 ml/37 ml), ethyl iodide (28.1 ml, 352 mmol) and 60% sodium hydride (5.28 g, 132 mmol) were added under cooling with ice and stirred at room temperature for 5.5 hours. Water was added slowly to the reaction mixture, followed by washing with ether. The aqueous layer was adjusted to pH 3 by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (n-hexane:ethyl acetate:acetic acid = 100:50:1), giving Z-N-Et-Phe(4-F)-OH (P3) (10.9 g, 72%).

Reference Example 9

15 Synthesis of Intermediate P10

To a solution of Boc-Phe(4-F)-OH (1.0 g, 3.53 mmol) in THF/DMF (6 ml/1.5 ml), ethyl iodide (2.24 ml, 20.8 mmol) and 60% sodium hydride (422 mg, 10.6 mmol) were added under cooling with ice and stirred at room temperature for 19 hours. The reaction mixture was mixed with water slowly and then with a saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The extract was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (n-hexane:ethyl acetate:methylene chloride = 1:1:15), giving Boc-N-Et-Phe(4-F)-OH (P10) (593 mg, 54%).

Reference Example 10

Synthesis of Intermediate T17

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A suspension of Z-N-Me-Phe(3-tBu-4-benzyloxy)-NH₂ (2.5 g, 5.27 mmol), a 35% aqueous formaldehyde solution (10 ml) and potassium carbonate (2.19 g, 15.8 mmol) in acetonitrile was stirred for 2 hours. The mixture was mixed with water, and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous NH₄Cl solution and then with saturated brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (n-hexane:ethyl acetate:methylene chloride = 1:1:1), giving Z-N-Me-Phe(3-tBu-4-benzyloxy)-NHCH₂OH (2.0 g).

To a solution of the above compound (2.0 g, 3.97 mmol) in 85% formic acid (30 ml), sodium methanesulfinate (1.5 g, 15.3 mmol) was added and then stirred at 50°C for 1 hour. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous NaHCO₃ solution, dried over anhydrous magnesium sulfate and concentrated under reduced pressure; to a solution of the thus obtained residue (1.8 g) in methanol (20 ml), 20% palladium hydroxide/carbon (0.50g) was added and stirred in a hydrogen atmosphere for 2 days. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated; the thus obtained residue was subjected to silica gel column chromatography (n-hexane:methanol:methylene chloride

=1:1:15), giving N-Me-Phe(3-tBu-4-benzyloxy)-NHCH₂SO₂CH₃,
(T17) (890 mg).

Reference Example 11

5 Synthesis of Intermediate T18

To a solution of Z-Tyr(3-tBu)-OMe (1.01 g, 2.62 mmol)
in methanol/water (12 ml/3 ml), lithium hydroxide
monohydrate (0.17 g, 3.93 mmol) was added and stirred at
room temperature for 2 hours. The reaction mixture was
10 washed with ether, rendered acidic by 2N hydrochloric acid
and extracted with methylene chloride. The extract was
dried over anhydrous magnesium sulfate and evaporated to
remove the solvent under reduced pressure, giving crude Z-
Tyr(3-tBu)-OH (0.98 g).

15 To a solution of the above crude compound (0.92 g,
2.48 mmol), WSCI (0.52 g, 2.73 mmol) and HOBt (0.37 g, 2.73
mmol) in DMF (15 ml), tert-butylamine (0.31 ml, 2.48 mmol)
and then NMM (0.29 ml, 2.73 mmol) were added under cooling
with ice and stirred at room temperature for 2 hours. The
20 reaction mixture was mixed with water, and extracted with
ethyl acetate. The organic layer was washed with 2N
hydrochloric acid, a saturated aqueous NaHCO₃ solution and
saturated brine in that order. The extract was dried over
anhydrous magnesium sulfate and concentrated under reduced
25 pressure; the thus obtained residue was subjected to silica
gel column chromatography (ethyl acetate:n-hexane = 1:2),
giving Z-Tyr(3-tBu)-NHtBu (1.05 g, 99%).

To a solution of the above compound (1.0 g, 2.34

mmol) in methanol (20 ml), 20% palladium hydroxide/carbon (0.16 g) was added and stirred in a hydrogen atmosphere for 2 hours. The reaction mixture was filtered with Celite and the filtrate was evaporated to remove the solvent under reduced pressure, giving crude Tyr(3-tBu)-NHtBu (T18) (0.60 g, 88%).

Reference Example 12

Synthesis of Intermediate T20

- 10 (1) Synthesis of 2-(4-benzyloxy-3-tert-butylphenyl)-N-benzyloxycarbonyl-N-methyl-1-methylethylamine

To a solution of Z-N-Me-Phe(3-tBu-4-benzyloxy)-OH (27.8 g, 58.5 mmol) in THF (290 ml), ethyl chloroformate (6.2 ml, 64.3 mmol) and N-methyl morpholine 7.7 ml, 70.2 mmol) were added under cooling with ice and stirred. After 2 hours, the reaction mixture was mixed with sodium borohydride (6.7 g, 175 mmol), water (100 ml) and methanol (100 ml) and stirred at room temperature for 6 hours. The reaction mixture was evaporated to remove the solvent under reduced pressure and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: methylene chloride:ethyl acetate:n-hexane = 1:1:2), giving 2-(4-benzyloxy-3-tert-butylphenyl)-N-benzyloxycarbonyl-1-hydroxymethyl-N-methylethylamine (12.4 g, 46%).

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A solution of the above compound (5.21 g, 11.2 mmol) in methylene chloride (55 ml), TEA (2.34 ml, 16.8 mmol) and methanesulfonyl chloride (0.954 ml, 12.3 mmol) were added under cooling with ice and stirred for 30 min. Under
5 cooling with ice, the reaction mixture was mixed with saturated aqueous NaHCO₃ and extracted with methylene chloride. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure,
10 giving a mesylate. To a solution of the mesylate in THF (30 ml), a 1M lithium triethyl borohydride/THF solution (22.4 ml, 22.4 mmol) was added. After 1 hour, further lithium triethylborohydride/THF solution (22.4 ml, 22.4 mmol) was added. After 30 min., the mixture was mixed with
15 water under cooling with ice and extracted with chloroform. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column
20 chromatography (developing solvent: ethyl acetate:n-hexane = 1:5), giving 2-(4-benzyloxy-3-tert-butylphenyl)-N-benzyloxycarbonyl-N-methyl-1-methylethylamine (3.42 g, 68%).
¹H-NMR(CDCl₃): δ 1.14(3H,d,J=6.9Hz), 1.36(9H,s), 2.50-2.80(2H,m), 2.76 and 2.83(total 3H,s), 4.30-4.58(1H,m),
25 4.88-5.10(4H,m), 6.74-7.14(3H,m), 7.20-7.50(10H,m)

(2) Synthesis of 2-(3-tert-butyl-4-hydroxyphenyl)-N-methyl-1-methylethylamine (T20)

A suspension of 2-(4-benzyloxy-3-tert-butylphenyl)-N-

benzyloxycarbonyl-N-methyl-1-methylethylamine (3.30 g, 7.35 mmol) and 20% palladium hydroxide/carbon catalyst (350 mg) in methanol (100 ml) was stirred in a hydrogen atmosphere for 1.5 hours. The mixture was filtered to remove the catalyst and the filtrate was evaporated to remove the solvent under reduced pressure, giving 2-(3-tert-butyl-4-hydroxyphenyl)-N-methyl-1-methylethylamine (T20) (1.62 g, 100%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 1.12(3H, d, $J=6.3\text{Hz}$), 1.38(9H, s), 2.42(3H, s),
10 2.64(2H, d, $J=6.6\text{Hz}$), 2.75-2.90(1H, m), 6.55(1H, d, $J=7.9\text{Hz}$),
6.84(1H, dd, $J=1.6, 7.9\text{Hz}$), 7.04(1H, d, $J=1.6\text{Hz}$).

Reference Example 13

Synthesis of Intermediate T21

15 (1) Synthesis of Z-N,O-dibenzyl-Tyr(3-tBu)-OMe

To a solution of Z-Tyr(3-tBu)-OMe (3.0 g, 7.78 mmol) in DMF (20 ml), under cooling with ice, sodium hydride (0.68 g, 17.1 mmol) was added and stirred for 15 min., followed by the addition of benzylbromide (2.3 ml, 19.5 mmol). The reaction mixture was stirred for 3 hours, mixed with a saturated aqueous NaHCO₃ solution and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:5), giving the titled compound (4.14 g, 94%).

(2) Synthesis of N-benzyl-2-(4-benzyloxy-3-tert-

methylethylamine

A suspension of N-benzyl-2-(4-benzyloxy-3-tert-butylphenyl)-1-methyl-N-(benzyloxycarbonyl)-ethylamine (2.35 g, 4.50 mmol) and 20% palladium hydroxide/carbon catalyst (0.50 g) in methanol (30 ml) was stirred in a hydrogen atmosphere overnight. The mixture was filtered to remove the catalyst and the filtrate was evaporated to remove the solvent under reduced pressure, giving 2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethylamine (T21) (0.90 g, 96%).

$^1\text{H-NMR}(\text{CDCl}_3): \delta$ 1.16(3H,d,J=6.6Hz), 1.39(9H,s), 2.45(1H,dd,J=4.9, 13.3Hz), 2.69(1H,dd,J=4.9,13.3Hz), 3.15(1H,m), 3.52H,brs), 6.58(1H,d,J=7.9Hz), 6.83(1H,dd,J=1.6,7.9Hz), 7.03(1H,d,J=1.6Hz).

Reference Example 14

Synthesis of Intermediate T23

To a solution of Tyr(3-tBu)-OMe (3.0 g, 11.9 mmol) in 1,4-dioxane/water (12 ml/12 ml), sodium carbonate (1.9 g, 17.9 mmol) and then ethyl chlorocarbonate (1.26 ml, 13.1 mmol) were added under cooling with ice and stirred for 2 hours. The reaction mixture was mixed with water, extracted with chloroform, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. To a solution of the thus obtained residue (3.85 g) in THF (120 ml), lithium aluminum hydride (2.83 g, 59.7 mmol) was added little by little and stirred at 60°C for 5 hours. The reaction mixture was poured into ice water,

6.98(1H,d,J=8.9Hz), 7.11(1H,d,J=8.2Hz), 7.13(1H,d,J=8.2Hz).

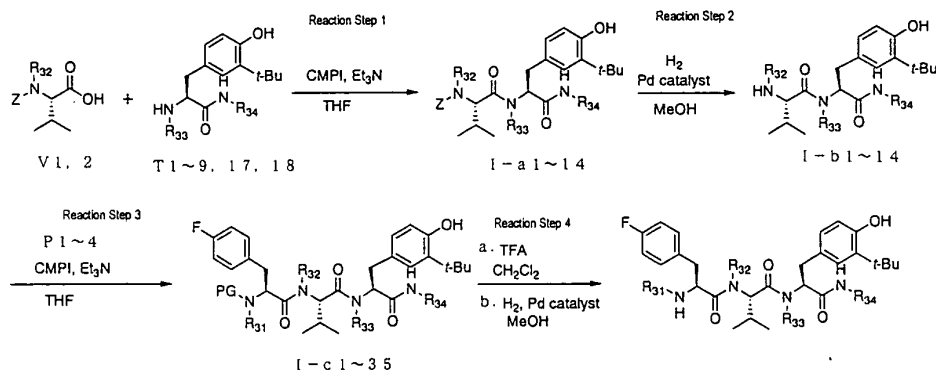
(2) Synthesis of 2-(4-fluorophenyl)-1-formylethylcarbamic acid tert-butyl ester (P11)

To a solution of the above compound (3.30 g, 10.1 mmol) in diethyl ether (150 ml), lithium aluminum hydride (498 mg, 13.1 mmol) was added under cooling with ice and stirred for 30 min. The reaction mixture was mixed with a solution of potassium hydrogen sulfate (2.75 g, 20.2 mmol) in water (20 ml) and stirred for 1 hour. The reaction mixture was filtered and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography (developing solvent: ethyl acetate:n-hexane = 1:5), giving the titled compound (2.37 g, 88%).

¹H-NMR(CDCl₃): δ 1.44(9H,s), 3.00-3.20(2H,m), 4.34-4.46(1H,m), 4.98-5.06(1H,m), 6.98(1H,d,J=8.6Hz), 7.01(1H,d,J=8.6Hz), 7.12(1H,d,J=8.3Hz), 7.14(1H,d,J=8.3Hz), 9.63(1H,s).

Scheme 1 shows the synthesis scheme of Examples 28-64.

Scheme 1: synthesis scheme of Examples 28-64



Synthesis process shown in scheme 1 is explained below:

5 Reaction step 1

To a solution of Compounds T and V and CMPI in THF, TEA was added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-a.

Reaction step 2

To a solution of Compound I-a in methanol, palladium catalyst was added and stirred at room temperature in a hydrogen atmosphere. The mixture was filtered to remove the palladium/carbon and the filtrate was evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-b.

Reaction step 3

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To a solution of Compounds I-b and P and CMPI in THF, TEA was added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed
5 with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-c.

10 Reaction step 4a (PG=Boc)

To a solution of Compound I-c in methylene chloride, TFA was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, alkalified by adding a saturated aqueous NaHCO_3 solution
15 and extracted with methylene chloride. The resultant was dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography, giving the titled compound.

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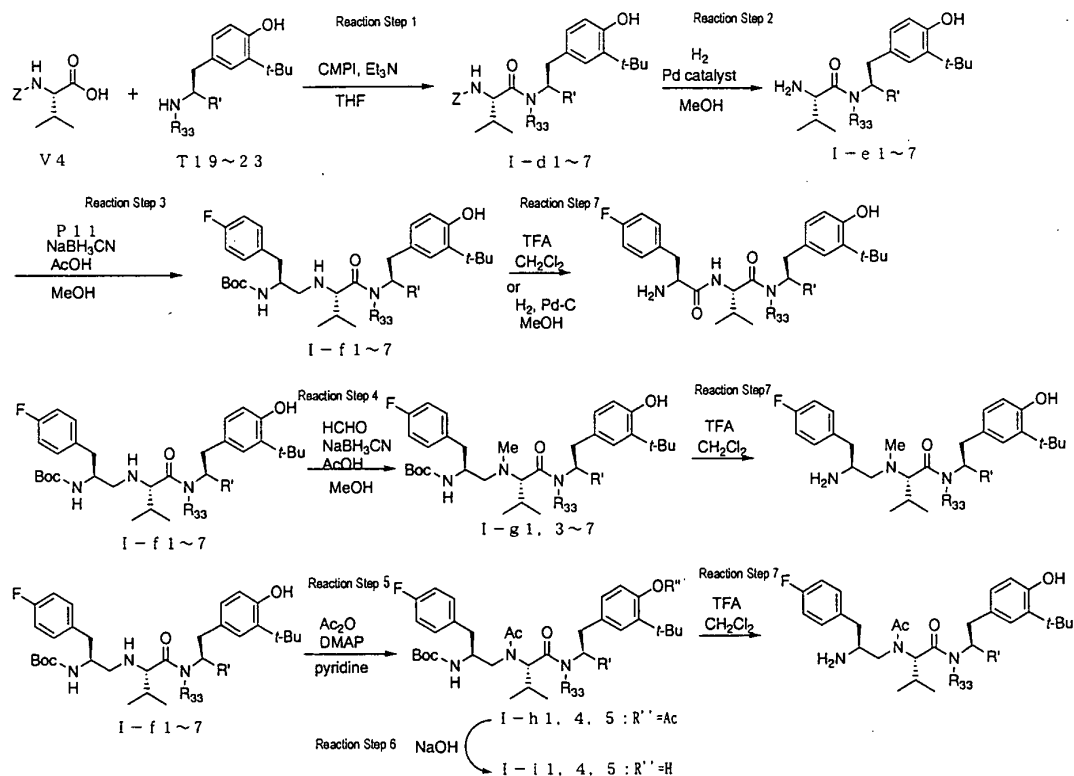
Reaction step 4b (PG=Z)

To a solution of Compound I-c in methanol, palladium catalyst was added and stirred at room temperature in a hydrogen atmosphere. The mixture was filtered to remove
25 the palladium/carbon and the filtrate was evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving the titled compound.

Scheme 2 shows the synthesis scheme of Examples 65-78.

Scheme 2: synthesis scheme of Examples 65-78

5



Synthesis process shown in scheme 2 is explained

10 below:

Reaction step 1

To a solution of Compounds T and V4 and CMPI in THF, TEA was added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and
15 extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium

sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-d.

Reaction step 2

5 To a solution of Compound I-d in methanol, palladium catalyst was added and stirred at room temperature in a hydrogen atmosphere. The mixture was filtered to remove the palladium catalyst and the filtrate was evaporated to remove the solvent under reduced pressure. The thus
10 obtained residue was subjected to silica gel column chromatography, giving Compound I-e.

Reaction step 3

 To a solution of Compounds P11 and I-e in methanol, acetic acid and sodium cyanoborohydride were added under
15 cooling with ice and stirred at room temperature. The reaction mixture was mixed with saturated aqueous NaHCO_3 and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced
20 pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-f.

Reaction step 4

 To a solution of Compound I-f in methanol, 35% aqueous formaldehyde solution, acetic acid and sodium
25 cyanoborohydride were added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with saturated aqueous NaHCO_3 and extracted with chloroform. The organic layer was washed with saturated

brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-g.

5 Reaction step 5

To a solution of Compound I-f in pyridine, acetic acid anhydride and 4-dimethylaminopyridine were added under cooling with ice and stirred at room temperature. The reaction mixture was mixed with water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous copper sulfate solution, water and saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-h.

15 Reaction step 6

To a solution of Compound I-h in methanol, a 2N aqueous sodium hydroxide solution was added and stirred at room temperature. The reaction mixture was mixed with saturated aqueous NH_4Cl and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated to remove the solvent under reduced pressure. The thus obtained residue was subjected to silica gel column chromatography, giving Compound I-i.

25 Reaction step 7

To a solution of Compound I-f, or I-g, or I-i in methylene chloride, TFA was added and stirred at room

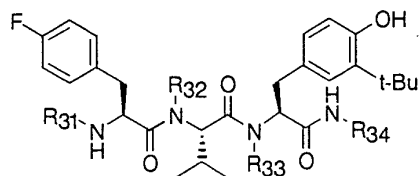
temperature. The reaction mixture was concentrated under reduced pressure, alkalified by adding a saturated aqueous NaHCO_3 solution and extracted with methylene chloride. The resultant was dried over anhydrous magnesium sulfate and
5 evaporated to remove the solvent under reduced pressure; the thus obtained residue was subjected to silica gel column chromatography, giving the titled compound.

Examples conducted according to Scheme 1 are shown in Tables D-1 to D-43.

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Table D-1

Structural Formula of Compounds of Example 28-64



Example 28

5 Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
H		Me		H		H		
Reaction 1								
Compound Tl:g	Compound Vl:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1	1.35	1.3	2.1	40	19	EA:H 3:1	I-a1	1.6
¹ H-NMR(CDCl ₃):δ 0.84 and 0.88(6H,d,J=6.6Hz), 1.36(9H,s), 2.15-2.35(1H,m), 2.75(3H,s), 2.8-3.1(2H,m), 4.02(1H,brd,J=11.2Hz), 4.5-4.7(1H,m), 5.13 and 5.15(2H,s), 5.3-5.5, 5.5-5.7, 5.8-6.0, 6.1-6.2, and 6.5-6.8(3H,m), 6.45(1H,d,J=7.9Hz), 6.81(1H,brd,J=7.9Hz), 7.07(1H,brs), 7.37(5H,s)								
Reaction 2								
Compound I-a1:g	Pd(OH) ₂ g	MeOH ml	Reaction time hr	Column sol.		Product	Amount g	
1.5	0.3	30	1	Not purified		I-b1	1.1	
¹ H-NMR(CDCl ₃):δ 0.65(3H,d,J=6.9Hz), 0.82(3H,d,J=6.9Hz), 1.37(9H,s), 1.8-2.0(1H,m), 2.30(3H,s), 2.74(1H,d,J=4.3Hz), 2.9-3.2(2H,m), 4.6-4.8(1H,m), 5.3-5.7(1H,m), 6.1-6.3(1H,m), 6.5-6.7(1H,m), 6.93(1H,brd,J=7.9Hz), 7.06(1H,brs), 7.6-7.8(1H,m)								

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Table D-2

Example 28(Continued from Table D-1)

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH₂

Reaction 3								
Compound I-b1:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.3	0.29	0.26	0.43	5	18	MC:M 20:1	I-c1	0.45
¹ H-NMR(CDCl ₃):δ 0.77, 0.89, and 1.01(6H,d,J=6.6Hz), 1.33, 1.36, 1.37, and 1.39(18H,s), 2.15-2.4(1H,m), 2.32 and 2.77(3H,s), 2.7-3.0(4H,m), 4.1-4.3, 4.5-4.6, and 4.6-4.8(2H,m), 5.36(1H,brd,J=8.9Hz), 5.44, 5.57, 5.71, 5.75, and 6.18(3H,brs), 6.6-7.2(7H,m), 7.8-7.9(1H,m)								
Reaction 4a								
Compound I-c1:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr		Column sol.	Amount g	HPLC min	
0.4	2	4	0.5		CH:M:N 400:10:1	0.32	17.8	
EI-MS(M ⁺):514								
¹ H-NMR(CDCl ₃):δ 0.71, 0.79, 0.91, and 0.92(6H,d,J=6.3-6.6Hz), 1.36 and 1.38(9H,s), 2.2-2.4(1H,m), 2.4-3.2(4H,m), 2.70 and 2.83(3H,s), 3.56 and 3.79(1H,dd,J=5.0-5.9,7.6Hz), 3.94 and 4.44(1H,d,J=10.9-11.2Hz), 4.56 and 4.74(1H,dd,J=6.6-8.9,14.2-16.2Hz), 5.47(1H,brs), 5.85 and 5.96(1H,brs), 6.4-6.9(3H,m), 6.9-7.2(5H,m), 9.01(1H,d,J=7.9Hz)								

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Table D-3

Example 29

Synthesis of N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
Me		Me		H		H		
Reaction 3								
Compound I-b1:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction Time hr	Column sol.	Product	Amount g
0.3	0.31	0.26	0.43	5	20	MC:M 20:1	I-C2	0.43
¹ H-NMR (CDCl ₃):δ 0.72, 0.79, and 0.92(6H, d, J=6.6Hz), 1.33, 1.34, 1.37, and 1.40(18H, s), 2.1-2.3(1H, m), 2.24 and 2.67(3H, s), 2.6-3.3(4H, m), 4.40 and 4.50(1H, d, J=10.9-11.6Hz), 4.5-4.8(1H, m), 4.8-4.9 and 5.0-5.2(1H, m), 5.49 and 5.98(2H, brs), 6.16(1H, s), 6.31(1H, brd, J=8.3Hz), 6.5-6.8(2H, m), 6.8-7.3(5H, m)								
Reaction 4a								
Compound I-c2:g	TFA ml	CH ₂ Cl ₂ ml	Reaction Time hr		Column sol.	Amount g	HPLC min	
0.35	1.5	3	0.5		CH:M:N 400:10:1	0.24	18.0	
EI-MS(M ⁺): 528								
¹ H-NMR(CDCl ₃):δ 0.52, 0.79, and 0.91(6H, d, J=5.0-6.9Hz), 1.33 and 1.39(9H, s), 2.1-2.3(1H, m), 2.24 and 2.36(3H, s), 2.56 and 2.61(3H, s), 2.6-3.2(4H, m), 3.54 and 3.61(1H, dd, J=5.9-6.3, 7.3-7.6Hz), 3.78 and 4.58(1H, d, J=10.9Hz), 4.49 and 4.68(1H, dd, J=7.3, 14.5Hz), 5.38, 5.58, 5.78, and 5.90(2H, brs), 6.6-7.2(7H, m), 9.07(1H, brd, J=7.6Hz)								

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Table D-4

Example 30

Synthesis of N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH₂

R ₃₁	R ₃₂	R ₃₃	R ₃₄
Et	Me	H	H

Reaction 3								
Compound I-b1:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.3	0.36	0.26	0.43	5	16	CH:M:N 400:10:1	I-c3	0.42

¹H-NMR(CDCl₃):δ 0.41, 0.67, and 0.86(6H,d,J=6.6Hz), 1.0-1.2(3H,m), 1.36(9H,s), 2.1-2.3(1H,m), 2.51 and 2.76(3H,s), 2.6-3.0 and 3.0-3.2(6H,m), 4.1-4.3(1H,m), 4.4-4.6(1H,m), 4.9-5.0 and 5.1-5.3(1H,m), 5.13(2H,s), 5.35(1H,brs), 5.76(2H,brs), 6.1-6.2 and 6.4-7.4(13H,m)

Reaction 4a						
Compound I-c3:g	Pd(OH) ₂ g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.37	0.07	5	1	CH:M:N 400:10:1	0.24	18.5

EI-MS(M⁺):542

¹H-NMR(CDCl₃):δ 0.39, 0.77, and 0.90(6H,d,J=6.3-6.9Hz), 1.05 and 1.16(3H,t,J=6.9Hz), 1.32 and 1.39(9H,s), 2.1-2.3(1H,m), 2.3-3.2(6H,m), 2.43 and 2.46(3H,s), 3.5-3.7(1H,m), 3.76 and 4.58(1H,d,J=10.9-11.5Hz), 4.47 and 4.68(1H,dd,J=7.0,13.9Hz), 5.42, 5.73, and 6.00(2H,brs), 6.6-7.2(7.8H,m), 8.74(0.2H,d,J=7.9Hz)

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Table D-5

Example 31

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
H		Me		H		Me		
Reaction 1								
Compound T2:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.07	1.36	1.31	1.79	43	2.5	EA:H 1:1	I-a2	2.11
EI-MS(M ⁺):497								
¹ H-NMR (CDCl ₃):δ 0.84 and 0.89(6H,d,J=6.6Hz), 1.36(9H,s), 2.12-2.30(1H,m), 2.71, 2.73, and 2.74(6H,s), 2.70-3.00(2H,m), 4.04(1H,d,J=11.2Hz), 4.40-4.58(1H,m), 4.82-4.86(1H,m), 5.19(2H,s), 5.70-5.80(1H,m), 6.43(1H,d,J=7.9Hz), 6.53(1H,d,J=8.2Hz), 6.80(1H,d,J=8.2Hz), 7.04(1H,s), 7.30-7.42(5H,m)								
Reaction 2								
Compound I-a2:g	Pd-C mg	MeOH ml	Reaction time hr	Column sol.	Product	Amount g		
2.01	200	50	2	C:M 20:1	I-b2	1.43		
EI-MS(M ⁺):363								
¹ H-NMR(CDCl ₃):δ 0.67 and 0.83(6H,d,J=5.9Hz), 1.37(9H,s), 1.84-2.02(1H,m), 2.31(3H,s), 2.73(1H,d,J=5.9Hz), 2.74(3H,d,J=5.0Hz), 2.90-3.08(2H,m), 4.52(1H,ddd,J=7.2,7.2,7.2Hz), 5.51(1H,brs), 5.98(1H,d,J=3.6Hz), 6.61(1H,d,J=7.9Hz), 6.91(1H,dd,J=2.0,7.9Hz), 7.04(1H,d,J=2.0Hz), 7.68(1H,d,J=7.9Hz)								

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Table D-6

Example 31(Continued from Table D-5)

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe

Reaction 3								
Compound I-b2:mg	Compound P1:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
400	387	337	0.46	11	13	EA:H 2:1	I-c4	652
EI-MS(M ⁺):628 ¹ H-NMR (CDCl ₃):δ 0.75, 0.77, 0.88, and 1.00(total 6H,d,J=5.3-6.3Hz), 1.36, 1.37 and 1.39(total 18H,s), 2.16-2.30(1H,m), 2.72(3H,d,J=4.6Hz), 2.70-3.22(7H,m), 4.38-4.80, and 5.10-5.22(total 3H,m), 5.28 and 5.32(total 1H,brs), 5.54-5.64(1H,m), 6.04-6.12(1H,m), 6.58-7.22(7H,m)								
Reaction 4a								
Compound I-c4:mg	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
564	2	8	1.5	MC:M 20:1	367	18.9		
EI-MS(M ⁺):528 ¹ H-NMR (CDCl ₃):δ 0.72,0.81 and 0.92(total 6H,d,J=6.3-6.6Hz), 1.36 and 1.38(total 9H,s), 2.20-2.40(1H,m), 2.50-3.24(10H,m), 3.59(2/3H,dd,J=5.6,7.6Hz), 3.73(1/5H,d,J=7.0Hz), 3.80(1/3H,dd,J=6.0,8.3Hz), 3.95(4/5H,d,J=8.9Hz), 4.40-4.54(2/5H,m), 4.63(3/5H,dd,J=6.6,14.2Hz), 5.65 and 5.78(total 1H,d,J=3.8-4.3Hz), 6.60(1/4H,d,J=8.3Hz), 6.70-7.16(7H,m), 9.07(3/4H,d,J=8.3Hz)								

TOTAL: 6729999

Table D-7

Example 32

Synthesis of N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄	
Me		Me		H		Me	
Reaction 3							
Compound I-b2:mg	Compound P2:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount mg
400	392	337	0.46	11	15	EA:H 1:1	I-c5 590
EI-MS(M ⁺):642 ¹ H-NMR(CDCl ₃):δ 0.72, 0.80, and 0.91(total 6H,d,J=6.2-6.6Hz), 1.23, 1.34, 1.37 and 1.39(total 18H,s), 2.06-2.30(1H,m), 2.25, 2.68, 2.75 and 2.86(total 6H,s), 2.79(3H,d,J=4.6Hz), 2.50-3.24(4H,m), 4.38-4.92 and 5.08-5.20(total 3H,m), 5.53 and 6.00(total 1H,brs), 5.88 and 6.21(total 1H,d,J=5.0- 8.3Hz), 6.52-7.22(7H,m)							
Reaction 4a							
Compound I-c5:mg	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount mg	HPLC min	
492	2	8	1	CH:M 20:1	305	18.9	
EI-MS(M ⁺):542 ¹ H-NMR(CDCl ₃):δ 0.57,0.79 and 0.91(total 6H,d,J=6.3-6.6Hz), 1.35 and 1.38(total 9H,s), 2.20-2.34(1H,m), 2.25 and 2.40(total 3H,s), 2.63 and 2.64(total 3H,s), 2.71 and 2.73(total 3H,d,J=4.3-4.6Hz), 2.60-3.10(4H,m), 3.55(1/2H,t,J=7.0Hz), 3.67(1/2H,t,J=6.9Hz), 3.81(1/2H,d,J=10.9Hz), 5.30-5.72(2H,m), 6.58-7.20(7H,m), 9.13(1/2H,d,J=8.6Hz)							

Table D-8

Example 33

Synthesis of N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
Et		Me		H		Me		
Reaction 3								
Compound I-b2:mg	Compound P3:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
490	559	414	0.45	8	13	EA:H 1:1	I-c6	747
¹ H-NMR(CDCl ₃):δ 0.40, 0.47, 0.67 and 0.86(total 6H,d,J=6.3-6.9Hz), 1.06-1.22(3H,m), 1.36 and 1.38(total 9H,s), 2.10-2.26(1H,m), 2.49 and 2.78(total 3H,s), 2.79 and 2.73(total 3H,d,J=4.6-4.9Hz), 2.60-3.40(6H,m), 4.28-4.44(2H,m), 4.90-5.16(3H,m), 5.40-5.68(2H,m), 6.38-7.42(12H,m)								
Reaction 4b								
Compound I-c6:mg	Pd-C mg	MeOH ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
660	66	10	12	CH:M:N 10:1:0.1	184	19.6		
EI-MS(M ⁺):556								
¹ H-NMR(CDCl ₃):δ 0.40, 0.77 and 0.89(total 6H,d,J=6.6Hz), 1.06 and 1.19(total 3H,t,J=7.0-7.3Hz), 1.34 and 1.38(total 9H,s), 2.10-2.28(1H,m), 2.48(3H,s), 2.30-3.20(6H,m), 2.73 and 2.74(total 3H,d,J=4.6Hz), 3.58-3.70(1H,m), 3.76(3/10H,d,J=11.2Hz), 4.38(7/10H,dt,J=4.9,7.3Hz), 4.50(7/10H,d,J=11.2Hz), 4.56(3/10H,dt,J=7.3,7.9Hz), 5.72-5.90(2/3H,m), 6.60-7.18(8H,m), 8.68(1/2H,d,J=7.9Hz)								

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Table D-9

Example 34

Synthesis of N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
Me		Me		Me		H		
Reaction 3								
CompoundI	Compound	CMPI	TEA	THF	Reaction	Column	Product	Amount
I-b3:g	P2:g	g	ml	ml	time hr	sol.		g
0.600	0.638	0.549	0.46	16	16	H:EA=2:1	I-c7	0.729
Reaction 4a								
Compound	TFA	CH ₂ Cl ₂	Reaction		Column	Amount		HPLC
I-c7:g	ml	ml	time hr		sol.	g		min
0.635	3.00	15	2		MC:M:H 10:1:1	0.413		19.6
EI-MS(M ⁺):542								
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.58, 0.81, 0.82 and 0.93(6H, d, J=6.4-6.9 Hz), 1.32 and 1.40(9H, s), 2.20-2.34(1H, m), 2.22 and 2.24(3H, s), 2.50 and 2.93(3H, s), 2.84 and 3.04(3H, s), 2.52 and 2.74(3H, d, J=6.5-6.9Hz), 3.18-3.41(1H, m), 3.42 and 3.62(1H, t, J=5.0-6.8Hz), 5.03 and 5.13(1H, d, J=10.7-10.9 Hz), 5.42-5.49(1H, m), 5.38 and 6.01(1H, brs), 6.38 and 6.62(1H, d, J=8.0Hz), 6.78-6.99(3H, m), 7.04-7.12(3H, m)								

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Table D-10

Example 35

Synthesis of N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄	
Et		Me		Me		H	
Reaction 3							
Compound I-b3:g	Compound P4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
0.460	0.520	0.420	0.53	10.0	17	H:EA 2:1	I-c8 0.300
Reaction 4a							
Compound I-c8:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.300	1.44	1.44	2	MC:M:H 10:1:1	0.200	20.2	
EI-MS(M ⁺):556							
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.54~1.1(6H, m and d, J=6.3Hz), 1.35 and 1.39(9H, s), 2.48 and 2.81(3H,s) 2.97 and 3.07(3H, s), 2.21 ~ 3.76(7H, m), 5.55~5.02(3H,m), 6.37 and 6.61(1H, d, J=8.3Hz), 6.78~7.21(6H, m)							

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Table D-11

Example 36

Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH-Me

R ₃₁		R ₃₂		R ₃₃		R ₃₄	
H		Me		Me		Me	
Reaction 1							
Compound T5:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reactio n time hr	Column sol.	Product Amount g
1.500	1.960	2.030	2.37	30.00	21	EA:H:MC 3:2:2	I-a4 2.200
Reaction 2							
Compound I-a4:g	Pd(OH) ₂ :g	MeOH ml	Reaction time hr	Column sol.		Product	Amount g
2.200	0.220	50.00	1	Not purified		I-b4	1.400
Reaction 3							
CompoundI I-b4:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
0.430	0.420	0.400	0.47	10.00	19	MC:M:H 10:1:3	I-c9 0.500
Reaction 4a							
Compound I-c9:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.500	2.50	2.50	1	MC:M:H 15:1:2	0.320	19.8	
EI-MS(M ⁺):542							
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.51~0.92(6H, d, J=6.6Hz), 1.32 and 1.37(9H, s), 2.24(2H, d, J=8.3Hz) 2.52 and 2.82 (3H, s) 2.18 ~ 3.89 (7H, m), 3.04 and 3.13 (3H, s), 5.42~4.82(3H,m), 6.41 and 6.63(1H, d, J=8.2Hz), 6.78~7.19(6H, m)							

Table D-12

Example 37

Synthesis of N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH-Me

R ₃₁		R ₃₂		R ₃₃		R ₃₄	
Me		Me		Me		Me	
Reaction 3							
CompoundI I-b4:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
0.430	0.440	0.400	0.47	10.00	19	EA:H:MC 2:1:1	I-c10 0.500
Reaction 4a							
Compound I-c10:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.500	2.50	2.50	1	MC:M:H 15:1:2	0.260	20.3	
EI-MS(M ⁺):556							
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.76~0.92(6H, m and d, J=6.3Hz), 1.34 and 1.39(9H, s), 2.25(3H, d, J=11.6Hz), 2.52 and 2.82(3H, s), 2.95 and 3.07(3H, s), 2.21 ~ 3.64(5H, m), 2.71 and 2.76(3H, d, J=4.3Hz), 5.42~5.01(3H,m), 6.37 and 6.54(1H, d, J=8.2Hz), 6.78~7.11(6H, m)							

Table D-13

Example 38

Synthesis of N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄	
Et		Me		Me		Me	
Reaction 3							
CompoundI I-b4:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
0.450	0.560	0.460	0.50	10.00	19	EA:H:MC 2:1:1	I-c11 0.450
Reaction 4a							
Compound I-c11:g	Pd(OH) ₂ :g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.450	0.050	15.00	1	MC:M:H 15:1:2	0.220	21.4	
EI-MS(M ⁺):570							
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.54~1.1(6H, m and d, J=6.3Hz), 1.26 and 1.34(9H, s), 2.77(3H,s), 2.97(3H, s), 3.07(3H, s), 2.12 ~ 3.72(7H, m), 5.38~5.21(3H,m), 6.37 and 6.54(1H, d, J=8.3Hz), 6.78~7.21(6H, m)							

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Table D-14

Example 39

Synthesis of Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
H		Me		Et		H		
Reaction 1								
Compound T7:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
4.000	5.720	5.510	6.02	100	24	EA:H:MC 2:1:1	I-a5	3.310
Reaction 2								
Compound I-a5 :g	Pd(OH) ₂ :g	MeOH ml	Reaction time hr		Column sol.	Product	Amount g	
3.100	0.300	70.00	1		MC:M:H 15:1:2	I-b5	1.600	
Reaction 3								
Compound d I-b5:g	Compound d P1:g	CMPI g	TEA ml	THF ml	Reactio n time hr	Column sol.	Produc t	Amount g
0.400	0.430	0.370	0.46	10.00	19	EA:H:MC 2:1:1	I-c12	0.380
Reaction 4a								
Compound I-c12:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr		Column sol.	Amount g	HPLC min	
0.380	1.50	1.50	2		MC:M:H 15:1:2	0.150	20.5	
EI-MS(M ⁺):542								
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.72~1.33(m, 9H), 1.35 and 1.39(9H, s), 2.24(2H, d, J=8.3Hz), 2.70 and 2.90(3H, s), 2.21 ~ 3.70 (7H, m) 4.92~5.23(3H, m), 6.41 and 6.61(1H, d, J=7.9Hz), 6.80~7.19(6H, m)								

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Table D-15

Example 40

Synthesis of N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄	
Me		Me		Et		H	
Reaction 3							
Compound I-b5:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
0.440	0.450	0.380	0.48	10.00	19	EA:H:MC 2:1:1	I-c13 0.220
Reaction 4a							
Compound I-c13:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.220	1.50	1.50	2	MC:M:H 15:1:2	0.130	21.0	
EI-MS(M ⁺):447							
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.72~0.95(6H, d, J=6.6Hz), 1.13~1.32(3H, m) 1.35 and 1.39(9H, s), 2.24(2H, d, J=8.3Hz) 2.21 ~ 3.96 (7H, m), 2.75 and 3.08 (3H, s), 4.92~5.40(3H, m), 6.41 and 6.63(1H, d, J=7.9Hz), 6.78~7.19(6H, m)							

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Table D-16

Example 41

Synthesis of N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄	
Et		Me		Et		H	
Reaction 3							
Compound I-b5:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
0.490	0.480	0.420	0.52	10.00	19	EA:H:MC 2:1:1	I-c14 0.260
Reaction 4a							
Compound I-c14:g	Pd(OH) ₂ :g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.260	0.030	10.00	2	MC:M:H 15:1:2	0.120	21.9	
EI-MS(M ⁺):570							
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.74~1.26(12H, m), 1.34 and 1.39(9H, s), 2.84 and 2.67(3H, s), 2.22~3.81(8H, m), 4.7~5.22(3H, m), 6.43 and 6.59(1H, d, J=7.9Hz), 6.81~7.19(6H, m)							

T0212T" 6T206860

Table D-17

Example 42

Synthesis of Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
H		Me		Et		Me		
Reaction 1								
Compound T8:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
4.20	4.80	4.62	6.31	75	13	EA:H 1:1	I-a6	4.33
EI-MS(M ⁺):585								
¹ H-NMR(CDCl ₃):δ 0.53, 0.80, 0.82 and 0.89(total 6H,d,J=6.3-6.6Hz), 0.96-1.30(3H,m), 1.34,1.36 and 1.36(total 9H,s), 2.20-2.40(1H,m), 2.46 and 2.75(total 3H,d,J=4.6Hz), 2.57 and 2.95(total 3H,s), 2.66-3.68(4H,m), 4.33, 4.45 and 4.59(total 1H,d,J=10.6Hz), 4.78-4.92(1H,m), 4.96-5.36(3H,m), 6.30-7.12(4H,m), 7.30-7.44(5H,m)								
Reaction 2								
Compound I-a6:g	Pd(OH) ₂ mg	MeOH ml	Reaction time hr	Column sol.	Product	Amount g		
2.81	280	60	1.5	CH:M 10:1	I-b6	2.10		
EI-MS(M ⁺):391								
¹ H-NMR(CDCl ₃):δ 0.34, 0.73, 0.90 and 0.96(total 6H,d,J=6.3-6.9Hz), 1.13 and 1.18(total 3H,t,J=6.9Hz), 1.36 and 1.37(total 9H,s), 1.60-1.80(1/2H,m), 2.14 and 2.27(total 3H,s), 2.10-2.30(1/2H,m), 2.58(1/2H,d,J=9.6Hz), 2.92-3.64(9/2H,m), 4.50-4.60(1/3H,m), 4.96-5.10(2/3H,m), 5.10-5.30(1H,m), 6.48(2/3H,brs), 6.54(1/3H,d,J=7.9Hz), 6.57(2/3H,d,J=7.9Hz), 6.79(1/3H,dd,J=2.0,7.9Hz), 6.91(2/3H,dd,J=2.0,7.9Hz), 7.00(1/3H,d,J=2.0Hz), 7.10(2/3H,d,J=2.0Hz), 8.24-8.34(1/3H,m)								

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Table D-18

Example 42(Continued from Table D-17)

Synthesis of Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

Reaction 3								
Compound I-b6:mg	Compound dP1:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
457	397	359	0.39	6	22	MC:M 20:1	I-c15	724
EI-MS(M ⁺):657								
¹ H-NMR(CDCl ₃):δ 0.72,0.78,0.82 and 0.89(total 6H,d,J=6.3-6.9Hz),1.08 and 1.16(total 3H,t,J=6.9Hz),1.33,1.36,1.38, and 1.39(total 18H,s),2.14-2.28(1H,m),2.54 and 2.98(total 3H,s),2.65 and 2.75(total 3H,d,J=4.6-4.9Hz),2.60-3.64(6H,m),4.58-5.18(4H,m),6.32-6.72(2H,m),6.90-7.18(5H,m)								
Reaction 4a								
Compound I-c15:mg	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
651	3	7	1	MC:M:H 20:1:1	354	21.5		
EI-MS(M ⁺):556								
¹ H-NMR(CDCl ₃):δ 0.67,0.82 and 0.92(total 6H,d,J=6.6Hz),1.10 and 1.15(total 3H,t,J=6.9Hz),1.34 and 1.39(total 9H,s),2.24-2.44(1H,m),2.67 and 2.76(total 3H,d,J=4.3-4.9Hz),2.73 and 3.05(total 3H,s),2.50-3.90(7H,m),4.94-5.08(2H,m),6.36-7.18(7H,m)								

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Table D-19

Example 43

Synthesis of N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂			R ₃₃		R ₃₄	
Me		Me			Et		Me	
Reaction 3								
Compound I-b6:mg	Compound P2:mg	CMPI mg	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
465	424	365	0.40	6	21	EA:H 2:1	I-c16	759
¹ H-NMR(CDCl ₃):δ 0.45, 0.73, 0.82 and 0.89(total 6H,d,J=6.4-6.9Hz), 1.02(3H,t,J=6.6Hz), 1.29, 1.36, 1.37, 1.39 and 1.42(total 18H,s), 2.20-2.30(1H,m), 2.36, 2.71, 2.93 and 3.67(total 6H,s), 2.77 and 2.90(total 3H,d,J=4.6-4.9Hz), 2.60-3.44(6H,m), 4.80-5.28(total 3H,m), 6.09(1H,d,J=4.0Hz), 6.19 and 6.35(total 1H,dd,J=1.3,7.3Hz), 6.51(1/2H,s), 6.60 and 6.69(total 1H,d,J=7.3Hz), 6.94-7.16(13/2H,m)								
Reaction 4a								
Compound I-c16:mg	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr		Column sol.		Amount mg	HPLC min
651	3	7	1		MC:M:H:N 10:1:1:0.1		457	22.1
EI-MS(M ⁺):570								
¹ H-NMR(CDCl ₃):δ 0.72, 0.83 and 0.92(total 6H,d,J=6.6Hz), 1.14 and 1.16(total 3H,t,J=6.6-6.9Hz), 1.34 and 1.39(total 9H,s), 2.23 and 2.27(total 3H,s), 2.20-2.40(1H,m), 2.55(1H,d,J=6.3Hz), 2.64-2.88(7H,m), 2.99(1H,dd,J=9.2,14.9Hz), 3.23(1H,dd,J=6.9,14.9Hz), 3.40-3.74(3H,m), 5.00-5.12(2H,m), 6.40 and 6.57(total 1H,d,J=7.9-8.2Hz), 6.44(1/2H,brs), 6.80(1/2H,dd,J=1.6,7.9Hz), 6.90-7.18(11/2H,m)								

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Table D-20

Example 44

Synthesis of N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
Et		Me		Et		Me		
Reaction 3								
Compound I-b6:mg	Compound P3:mg	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
640	675	501	0.55	9	17	EA:H 1:1	I-c 17	963
¹ H-NMR(CDCl ₃):δ 0.71, 0.78, 0.88, 1.07 and 1.09(total 6H,d,J=6.3-6.9Hz), 0.98 and 1.18(total 3H,t,J=6.9Hz), 1.29, 1.35 and 1.39(total 9H,s), 2.14-2.30(1H,m), 2.48-3.56(14H,m), 4.78(1H,d,J=10.6Hz), 4.86-5.24(3H,m), 5.98-6.10(3/2H,m), 6.21(1H,s), 6.59 and 6.64(total 1H,d,J=7.9Hz), 6.84-7.20(11/2H,m), 7.30-7.44(5H,m)								
Reaction 4b								
Compound I-c17:mg	Pd(OH) ₂ mg	MeOH ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
870	87	15	15	CH:M 10:1	252	22.9		
EI-MS(M ⁺):584								
¹ H-NMR(CDCl ₃): δ 0.73, 0.82 and 0.91(total 6H,d,J=6.3-6.6Hz), 1.01, 1.06, 1.13 and 1.16(total 6H,t,J=6.6-6.9Hz), 1.34 and 1.39(total 9H,s), 2.20-3.04(5H,m), 2.67 and 2.78(total 3H,s), 2.69 and 2.74(total 3H,d,J=4.6-4.9Hz), 3.26(1H,dd,J=7.9,14.2Hz), 3.45(1H,dd,J=8.9,13.2Hz), 3.54-3.74(2H,m), 4.94-5.12(5/2H,m), 5.38-5.46(1/2H,m), 6.42 and 6.57(total 1H,d,J=7.9-8.3Hz), 6.80-7.16(6H,m)								

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Table D-21

Example 45

Synthesis of Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
H		Et		H		H		
Reaction 1								
Compound T1:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
3.3	4.29	4.0	4.3	80	2	EA:H 3:1	I-a7	6.5
¹ H-NMR(CDCl ₃): δ 0.7-1.0(9H,m), 1.2-1.4(9H,m), 2.2-2.4(1H,m), 2.8-3.0(1H,m), 3.0-3.15(1H,m), 3.2-3.35(2H,m), 3.6-3.7(1H,brd,J=10.9Hz), 4.45-4.6(1H,m), 5.04(1H,brs), 5.15(1H,s), 5.15-5.25(1H,m), 6.02(1H,brs), 6.47(1H,brd,J=7.3Hz), 6.86(1H,brd,J=7.3Hz), 7.0-7.2(2H,m), 7.3-7.5(5H,m)								
Reaction 2								
Compound I-a7:g	Pd(OH) ₂ g	EtOH ml	Reaction time hr	Column sol.	Product	Amount g		
6.4	1.2	130	1.5	Not purified	I-b7	4.37		
¹ H-NMR(CDCl ₃): δ 0.63(3H,d,J=6.6Hz), 0.83(3H,d,J=6.6Hz), 1.03(3H,t,J=6.9z), 1.37(9H,s), 1.85-2.05(1H,m), 2.4-2.6(2H,m), 2.86(1H,d,J=4.0Hz), 2.9-3.2(2H,m), 4.6-4.8(1H,m), 5.55(1H,brs), 6.22(1H,brs), 6.4-6.6(1H,m), 6.64(1H,d,J=7.3Hz), 6.92(1H,brd,J=7.3Hz), 7.05(1H,brs), 7.90(1H,brd,J=8.3Hz)								

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Table D-22

Example 45(Continued from Table D-21)

Synthesis of Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH₂

Reaction 3								
Compound I-b7:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1	1.17	1.06	1.7	4	13	EA:H 1:2	I-c18	0.56
¹ H-NMR(CDCl ₃):δ 0.3-0.9(9H,m), 1.2-1.5(18H,m), 2.2-2.4(1H,m), 2.6-3.4(6H,m), 3.9-4.1, 4.4-4.8, and 4.8-4.9(3H,m), 5.53(1H,brs), 6.25(1H,brs), 6.25-6.45(2H,m), 6.56(1H,brs), 6.6-6.9(1H,m), 6.9-7.1(3H,m), 7.15-7.3(2H,m), 7.6-7.8(1H,m)								
Reaction 4a								
Compound I-c18 g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount g	HPLC min		
0.51	2	4	1	MC:M 20:1	0.36	19.9		
EI-MS(M ⁺):528 ¹ H-NMR(CDCl ₃):δ 0.60(3H,d,J=6.6Hz), 0.8-0.9(6H,m), 1.38(9H,s), 2.2-2.4(1H,m), 2.68(1H,dd,J=7.3,13.5Hz), 2.8-3.0(2H,m), 3.0-3.25(3H,m), 3.71(1H,t,J=6.9Hz), 4.21(1H,brd,J=10.9Hz), 4.4-4.6(1H,m), 5.55(1H,brs), 6.23(1H,brs), 6.64(1H,d,J=7.9Hz), 6.86(1H,dd,J=1.7,7.9Hz), 6.9-7.0(1H,m), 6.97(2H,t,J=8.6Hz), 7.0-7.2(3H,m)								

Table D-23

Example 46

Synthesis of N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
Me		Et		H		H		
Reaction 3								
Compound I-b7:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.0	1.23	1.06	1.7	4	14	MC:M 50:1	I-c 19	0.54
Reaction 4a								
Compound I-c19:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr		Column sol.	Amount g	HPLC min	
0.48	2	4	0.5		MC:M 20:1	0.26	20.4	
EI-MS(M ⁺):542								
¹ H-NMR(CDCl ₃):δ 0.57, 0.68, 0.71, and 0.91(6H,d,J=6.6Hz), 0.99 and 1.05(3H,t,J=6.9Hz), 1.37(9H,s), 2.29 and 2.38(3H,s), 2.3-2.5(1H,m), 2.8-3.4(6H,m), 3.52 and 3.60(1H,t,J=6.6Hz), 3.6-3.9(1H,m), 4.5-4.7(1H,m), 5.66, 5.74, 5.83, and 6.25(2H,brs), 6.66-6.72(7H,m), 7.61(1H,brd,J=5.4Hz), 9.16(1H,d,J=7.6Hz)								

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Table D-25

Example 48

Synthesis of Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
H		Et		H		Me		
Reaction 1								
Compound T2:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
4.95	6.62	6.57	8.3	120	2	EA:H 3:2	I-a8	9.0
Reaction 2								
Compound I-a8:g	Pd(OH) ₂ g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g		
8.9	0.90	200	1.5	Not purified	I-b8	6.4		
¹ H-NMR(CDCl ₃):δ 0.64(3H,d,J=6.9Hz), 0.84(3H,d,J=6.9Hz), 1.05(3H,t,J=7.1Hz), 1.37(9H,s), 1.90-2.02(1H,m), 2.51(2H,q,J=6.9Hz), 2.73(3H,d,J=4.9Hz), 2.86(1H,d,J=4.3Hz), 2.91-3.07(2H,m), 4.53(1H,dd,J=7.2,15.2Hz), 6.04(1H,brd,J=4.6Hz), 6.63(1H,d,J=7.9Hz), 6.91(1H,dd,J=2.0,7.9Hz), 7.03(1H,d,J=2.0Hz), 7.88(1H,d,J=8.3Hz)								

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Table D-28

Example 50

Synthesis of N-Et-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
Et		Et		H		Me		
Reaction 3								
Compound I-b8:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
1.52	1.53	1.13	1.23	20	96	EA:H 1:1	I-c23	520
¹ H-NMR (CDCl ₃):δ 0.41, 0.57, 0.62 and 0.72(total 6H,d,J=6.3-6.9Hz), 0.80-1.20(total 6H,m), 1.35, 1.38 and 1.40(total 9H,s), 2.22-2.42(1H,m), 2.66(3H,d,J=4.3Hz), 2.74-3.56(8H,m), 4.37(1H,dd,J=7.3,7.9Hz), 5.00-5.48(4H,m), 5.78-6.00(1H,m), 6.50-6.66(1H,m), 6.84-7.44(11H,m)								
Reaction 4b								
Compound I-c23:mg	Pd(OH) ₂ mg	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min		
450	45	8	14	MC:M:N 20:1:1	308	21.6		
EI-MS(M ⁺):570								
¹ H-NMR (CDCl ₃):δ 0.47, 0.64, 0.70 and 0.76(total 6H,d,J=6.3-6.6Hz), 0.88-1.24(6H,m), 1.38(9H,s), 2.10-2.64(3H,m), 2.70 and 2.71(total 3H,d,J=4.6Hz), 2.80-3.30(6H,m), 3.58-3.94(2H,m), 4.46(1H,dd,J=7.6-7.9Hz), 5.74-6.08(2H,m), 6.61(1H,d,J=7.9Hz), 6.78-7.20(6H,m), 7.38(1/2H,d,J=6.3Hz), 8.74(1/2H,d,J=7.9Hz)								

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Table D-29

Example 51

Synthesis of Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH₂

SYNTHESIS OF 1,1,1,3,3,3-Hexafluoro-4-iodo-4-methylbutane

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
H		Et		Me		H		
Reaction 1								
Compound T4:g	Compound V2 :g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
3.360	4.500	4.113	3.73	110	20	H:ACT 3:2	I-a9	5.970
Reaction 2								
Compound I-a9:g	Pd-C g	MeOH ml	Reaction time hr		Column sol.	Product	Amount g	
5.870	1.000	114	1		Not purified	I-b9	3.600	
Reaction 3								
CompoundI I-b9:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.200	1.350	1.220	1.33	6	18	H:EA 2:1	I-c24	1.160
Reaction 4a								
Compound I-c24:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr		Column sol.	Amount g	HPLC min	
1.06	5.00	10	1.5		MC:M: H 15:1:2	0.251	19.3	
EI-MS(M ⁺):542								
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.30, 0.69, 0.82 and 0.85(6H,d, J=6.4-6.9 Hz), 0.92 and 1.12(3H,t,J=3.4-4.1Hz), 1.35 and 1.37(9H,s), 2.25-2.40(1H,m), 2.56-3.37(5H,m), 2.82 and 3.02(3H,s), 3.60-3.77(2H,m), 4.83-5.38(2H,m), 6.02band 6.18(2H,brs), 6.43 and 6.62(1H,d,J=6.8Hz), 6.82-7.15(6H,m)								

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Table D-30

Example 52

Synthesis of N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄	
Me		Et		Me		H	
Reaction 3							
Compound I I-b9:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
1.200	1.420	1.220	1.33	7	30	H:EA 1:2	I-c25 0.740
Reaction 4a							
Compound I-c25:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.674	3.00	10	2	MC:M:H 10:1:2	0.278	20.0	
EI-MS(M ⁺):556							
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.42, 0.78, 0.84 and 0.91(6H,d, J=6.3-6.9 Hz), 0.94 and 1.18(3H, t, J=3.6Hz), 1.35 and 1.37(9H, s), 2.20-2.34(1H,m), 2.29(3H,s), 2.62-3.02(4H,m), 2.93 and 3.04(3H,s), 3.17-3.31(2H,m), 3.45-3.72(1H,m), 5.02 and 5.22(1H, d,J=10.7-10.9 Hz), 5.09 and 5.17(1H,t,J=5.8-6.1Hz), 5.69, 6.07 and 6.57(2H,brs), 6.45 and 6.64(1H,d,J=8.0Hz), 6.78-7.14(6H,m)							

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Table D-31

Example 53

Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄	
Et		Et		Me		H	
Reaction 3							
Compound I I-b9:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
1.020	1.640	1.220	1.33	8	12	MC:M:H 20:1:1	I-c26 1.040
Reaction 4b							
Compound I-c26:g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.934	0.093	20	3	MC:M:H =15:1:2	0.201 0.103	20.7 22.4	
Compound of which yeilded amount was 0.201 g with HPLC retention time of 20.7 min.							
EI-MS(M ⁺):570							
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.42,0.79,0.84 and 0.91(6H,d and m, J=6.3-6.9Hz), 1.02 and 1.11(6H,t,J=3.6Hz), 1.33 and 1.40(3H,s), 2.20-3.36(9H,m), 2.92 and 3.03(3H,s), 3.51-3.75(1H,m), 5.00-5.38(2H,m), 6.02 and 6.58(2H,brs), 6.42-6..62(1H, d, J=8.0Hz), 6.82-7.20(6H, m)							
Compound of which yeilded amount was 0.103 g with HPLC retention time of 22.4 min.							
EI-MS(M ⁺):570							
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.13 and 0.79(4H, t, J=3.4 Hz), 0.62 and 0.89(2H, d, J=6.3-6.9Hz), 0.97 and 1.05(6H,t,J=3.6Hz), 1.34 and 1.41(9H,s), 1.92-2.03(1H,m), 2.21-2.60(2H, m), 3.00 and 3.08(3H,s), 2.74-3.25(4H,m), 3.60-3.72(1H,m), 4.62(1H,d,J=8.0Hz), 4.78-4.82(1H,m), 5.18-5.36(2H,m), 6.02(1H,brs), 6.59 and 6.63(1H,d,J=8.0Hz), 6.81-6.98(3H,m), 7.09-7.20(3H,m)							

[illegible][illegible][illegible][illegible]

Table D-33

Example 54(Continued from Table D-32)

Synthesis of Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe

Reaction 3										
Compound I-b10:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg		
1.15	1.25	1.13	1.23	20	13	EA:H 2:1	I-c27	434		
Reaction 4a										
Compound I-c27:mg	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount mg	HPLC min				
434	2	2	2.5	EA:EtOH =10:1	86.0 26.8	20.6 22.8				
Compound of which yeilded amount was 86.0 mg with HPLC retention time of 20.6 min. EI-MS(M ⁺):556 ¹ H-NMR(CDCl ₃):δ 0.27-1.18(9H,m), 1.35,1.39(9H,s), 2.15-3.77(12H,m), 2.84, 3.06(3H,s), 4.87-5.27(2H,m), 5.99-7.20(8H,m)										
Compound of which yeilded amount was 26.8 mg with HPLC retention time of 22.8 min. EI-MS(M ⁺):556 ¹ H-NMR(CDCl ₃): δ 0.16, 0.40, 0.55, 0.84(6H,d,J=6.3-6.9Hz), 0.83, 1.01(3H,t,J=7.1Hz), 1.36,1.41(9H,s), 2.00-2.21(1H,m), 2.67,2.76(3H,d,J=4.8Hz), 3.05,3.09(3H,s), 2.81-3.30(7H,m), 3.68-3.87(1H,m), 3.72, 3.80(1H,dd,J=7.8,6.1Hz), 4.61, 5.10(1H,d,J=10.7Hz), 4.66, 5.24(1H,dd,J=9.7,6.4Hz), 6.05-7.20(8H,m)										

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Table D-34

Example 55

Synthesis of N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
Me		Et		Me		Me		
Reaction 3								
Compound I-b10:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
1.0	1.14	0.98	1.07	17	14	EA:H 2:1	I-c28	322
Reaction 4a								
Compound I-c28:mg	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
322	2	2	2	EA:EtOH 10:1	101 38	21.1 22.6		
Compound of which yeilded amount was 101 mg with HPLC retention time of 21.1 min.								
EI-MS(M ⁺):570								
¹ H-NMR (CDCl ₃):δ 0.41, 0.79, 0.86, 0.90(6H,d,J=6.3-6.9Hz), 0.94, 1.15(3H,t,J=7.3Hz), 1.34, 1.39(9H,s), 2.27, 2.28(3H,s), 2.71, 2.76(3H,d,J=4.8Hz), 2.15-3.78(9H,m), 2.93,3.08(3H,s), 4.98-5.32(2H,m), 6.03-7.20(8H,m)								
Compound of which yeilded amount was 38 mg with HPLC retention time of 22.6 min.								
EI-MS(M ⁺):570								
¹ H-NMR (CDCl ₃): δ 0.10, 0.14, 0.63, 0.85(6H,d,J=6.3-6.9Hz), 0.82, 0.95(3H,t,J=7.1Hz), 1.35, 1.40(9H,s), 2.18, 2.54(3H,s), 2.71, 2.75(3H,d,J=4.8Hz), 2.99, 3.08(3H,s), 1.89-3.27(8H,m), 3.46-3.64(1H,m), 4.54, 5.19(1H,d,J=10.6Hz), 4.66, 5.23(1H,t,J=7.3Hz), 6.51, 6.60(1H,d,J=7.9Hz), 6.07-7.20(7H,m)								

TOTAL "67206960

Table D-35

Example 56

Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
Et		Et		Me		Me		
Reaction 3								
Compound I-b10:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount mg
1.0	1.32	0.98	1.07	17	14	EA:H 2:1	I-c29	576
Reaction 4b								
Compound I-c29:mg	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
576	0.05	5	3	EA:EtOH 15:1	192 129	22.0 23.6		
Compound of which yeilded amount was 192 mg with HPLC retention time of 22.0 min.								
EI-MS(M ⁺):584								
¹ H-NMR (CDCl ₃):δ 0.41-1.18(12H,m), 1.35, 1.39(9H,s), 2.12-4.13(14H,m), 2.92,3.08(3H,s), 4.99-5.27(2H,m), 6.00-7.20(8H,m)								
Compound of which yeilded amount was 129 mg with HPLC retention time of 23.6 min.								
EI-MS(M ⁺):584								
¹ H-NMR (CDCl ₃):δ 0.12-1.30(12H,m), 1.36, 1.41(9H,s), 1.93-4.16(14H,m), 2.99,3.07(3H,s), 4.57-5.23(2H,m), 5.40-7.22(8H,m)								

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Table D-36

Example 57

Synthesis of Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄	
H		Et		Et		H	
Reaction 1							
Compound d T7:g	Compound d V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
16.000	24.088	23.200	25.32	400.00	60	EA:H:MC 3:2:2	I-a11 16.000
Reaction 2							
Compound I-a11:g	Pd(OH) ₂ :g	MeOH ml	Reaction time hr	Column sol.	Product Amount g		
9.000	0.900	200.00	2	MC:M:H 15:1:2	I-b11 4.000		
Reaction 3							
Compound I-b11:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g
1.100	1.150	1.040	1.13	10.00	72	EA:H:MC 3:2:2	I-c30 0.700
Reaction 4a							
Compound I-c30:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount g	HPLC min	
0.650	2.00	2.00	2	MC:M:H 15:1:2	0.180	20.9	
EI-MS(M ⁺):542							
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.51, 0.82, 0.87 and 0.94(6H,d,J=6.6~6.9Hz), 0.82~1.31(6H,m), 1.35 and 3.81(9H,s), 2.21~3.82 (9H,m) 4.83~5.30(3H,m), 6.62 and 6.54(1H,d,J=7.9Hz), 6.80~7.21(6H,m)							

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Table D-37

Example 58

Synthesis of N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
Me		Et		Et		H		
Reaction 3								
Compound I-b11:g	Compound P2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.240	1.360	1.170	1.28	10.00	72	EA:H:MC 3:2:2	I-c31	0.300
Reaction 4a								
Compound I-c31:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount g	HPLC min		
0.280	2.00	2.00	2	MC:M:H 15:1:2	0.170	21.2		
EI-MS(M ⁺):570								
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.63~1.30(9H, m and d, J=6.3Hz),, 1.34 and 1.39(9H, s), 2.30(3H,s), 2.22~3.90(9H,m), 4.97~5.33(3H,m), 6.43 and 6.62(1H,d,J=7.92), 6.81~7.19(6H, m)								

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Table D-38

Example 59

Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH₂

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
Et		Et		Et		H		
Reaction 3								
Compound I-b11:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.500	1.980	1.470	1.60	10.00	72	EA:H:MC 3:2:2	I-c32	0.700
Reaction 4b								
Compound I-c32:g	Pd(OH) ₂ :g	MeOH ml	Reaction time hr	Column sol.	Amount g	HPLC min		
0.650	0.065	10.00	2	MC:M:H 15:1:2	0.240	20.0		
EI-MS(M ⁺):458 ¹ H-NMR (CDCl ₃): (two rotamers) δ 0.85~1.27(15H, m), 1.37 and 1.39(9H, s), 2.03~3.63(11H, m), 4.50~4.55(1H, m), 5.02~5.34(2H, m), 6.43 and 6.60(1H, d, J=8.24), 6.81~7.19(6H, m)								

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Table D-39

Example 60

Synthesis of Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄			
H		Et		Et		Me			
Reaction 1									
Compound T8:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g	
10.000	15.000	14.000	14.96	357	48	H:EA 2:1	I-a12	5.610	
Reaction 2									
Compound I-a12:g	Pd-C g	MeOH ml	Reaction time hr		Column sol.	Product	Amount g		
5.500	1.000	100	2		H:ACT 1:1	I-b12	2.950		
Reaction 3									
Compound I-b12:g	Compound d P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g	
0.900	0.943	0.850	0.93	6	48	CH:M:N 300:10:1	I-c33	0.750	
Reaction 4a									
Compound I-c33:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr		Column sol.	Amount g	HPLC min		
0.742	4.00	6	2		CH:M:N 300:10:1	0.210	22.0		
EI-MS(M ⁺):570									
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.64 and 0.78-1.20(12H, d and m, J=7.0-7.9Hz), 1.24 and 1.37(9H, s), 2.20-2.40(1H, m), 2.62-3.08(4H, m), 3.19-3.46(3H, m), 3.57-3.89(2H, m), 4.62-5.11(2H, m), 6.44-6.62(2H, m), 6.79-7.13(5H, m)									

T0227T" 6T206260

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Table D-41

Example 62

Synthesis of N-Et-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHMe

R ₃₁		R ₃₂		R ₃₃		R ₃₄			
Et		Et		Et		Me			
Reaction 3									
Compound I I-b12:g	Compound P3:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product Amount g		
1.000	1.277	0.945	1.10	6.00	48	MC:M:H 20:1:1	I-c35 0.540		
Reaction 4b									
Compound I-c35:g	Pd-C g	MeOH ml	Reaction time hr		Column sol.	Amount g	HPLC min		
0.501	0.050	67	2		MC:M:H 25:1:3	0.240	23.2		
EI-MS(M ⁺):598									
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.64 and 0.84-0.92(6H, d and m, J=7.9Hz), 1.04, 1.05 and 1.13(6H,t,J=6.3Hz), 1.33 and 1.39(3H, s), 2.21-2.94(6H,m), 3.12-3.80(6H,m), 4.82-5.08(1H, m), 5.13 and 5.20(1H,d,J=9.7Hz), 6.47 and 6.58(1H,d,J=8.8Hz), 6.79-7.19(6H,m)									

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Table D-42

Example 63

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHtBu

R ₃₁		R ₃₂		R ₃₃		R ₃₄			
H		Me		H		tBu			
Reaction 1									
Compound T18:g	Compound V2:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g	
0.58	0.55	0.56	0.61	10	2	EA:H 1:3	I-a13	1.0	
Reaction 2									
Compound I-a13:g	Pd(OH) ₂ g	MeOH ml	Reaction time hr		Column sol.	Product	Amount g		
1.0	0.16	20	5		Not purified	I-b13	0.75		
Reaction 3									
Compound I-b13:g	Compound P1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g	
0.37	0.34	0.33	0.38	4	14	MC:M:N 50:1:0. 1	I-c36	0.58	
Reaction 4a									
Compound I-c36:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time min		Column sol.	Amount g	HPLC min		
0.49	2	4	30		MC:M:N 30:1:0.1	0.31	23.4		
EI-MS(M ⁺):570									
¹ H-NMR(CDCl ₃):δ 0.72(2H,d,J=6.9Hz), 0.82(1H,d,J=6.6Hz), 0.92-0.96(3H,m), 1.19(3H,s), 1.22(6H,s), 1.37(3H,s), 1.38(6H,s), 2.2-2.4(1H,m), 2.5-3.0(32/5H,m), 3.17(3/5H,dd,J=4.9,13.9Hz), 3.61(3/5H,br), 3.82(2/5H,br), 3.96(3/5H,d,J=10.9Hz), 4.3-4.6(7/5H,m), 5.25(1/3H,s), 5.41(1/3H,br), 5.48(2/3H,s), 6.03(2/3H,br), 6.6-6.8(2H,m), 6.9-7.2(5H,m), 9.00(1H,d,J=7.9Hz)									

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Table D-43

Example 64

Synthesis of Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH₂SO₂CH₃

R ₃₁		R ₃₂		R ₃₃		R ₃₄		
H		Me		Me		CH ₂ SO ₂ CH ₃		
Reaction 1								
Compound T17:g	Compound V1:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.840	0.782	0.753	0.8 2	10	15	EA:H:MC 3:2:2	I-a14	1.200
Reaction 2								
Compound I-a14:g	Pd(OH) ₂ :g	MeOH ml	Reaction time hr		Column sol.	Product	Amount g	
1.100	0.150	30.00	2		Not purified	I-b14	0.850	
Reaction 3								
CompoundI I-b14:g	Compound :g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
0.850	0.710	0.572	0.62	10.00	17	EA:H:MC 1:1:1	I-c37	1.020
Reaction 4a								
Compound I-c37:g	Pd(OH) ₂ :g	MeOH ml	Reaction time hr		Column sol.	Amount g	HPLC min	
1.020	0.150	30.00	2		MC:M:H 15:1:2	0.530	20.2	
EI-MS(M ⁺):620								
¹ H-NMR (CDCl ₃): (two rotamers) δ 0.78(3H, dd, J=6.6, 12.1Hz), 0.91(3H, dd, J=6.6, 11.2Hz), 1.26 and 1.35(9H, s), 2.00(3H,s), 2.55, 2.63, 2.75, 2.84, 2.99 and 3.16(8H,s), 2.21 ~ 5.30(11H, m), 6.43 and 6.55(1H, d, J=7.9Hz), 6.76~7.13(6H, m)								

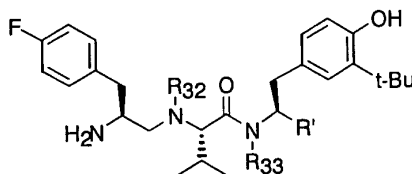
- 5 Examples of compounds synthesized according to the scheme 2 are shown in Tables D-44 to D-66.

Table D-44

Example 65

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoyl-ethyl)-N-methyl-3-methylbutanamide

Structural Formula of Compounds of Example 65-78



R ₃₂		R ₃₃		R'				
H		Me		CONH ₂				
Reaction 1								
Compound T4:g	Compound V4:g	CMPI :g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
5.78	6.97	7.08	8.05	115	19	EA:H 1:1	I-d1	9.50
¹ H-NMR(CDCl ₃):δ 0.63, 0.74, 0.89 and 0.94(total 6H,d,J=6.6-6.9Hz), 1.36 and 1.39(total 9H,s), 1.90-2.04(1H,m), 2.80-3.38(2H,m), 2.96 and 3.04(total 3H,s), 4.14-4.22(1/2H,m), 4.40-4.50(1/2H,m), 4.60-4.70(1/2H,m), 4.88-5.40(11/2H,m), 5.88(1/2H,brs), 6.49(1/2H,d,J=7.9Hz), 6.58(1/2H,d,J=7.9Hz), 6.87(1H,d,J=7.9Hz), 7.02-7.14(1H,m), 7.30-7.40(5H,m)								
Reaction 2								
Compound I-d1:g	Pd-C g	MeOH ml	Reaction time hr	Crude Compound I-e1 was used in Reaction 3.				
4.23	0.50	100	2					

Variable	Mean	SD	Min	Max
Age	38.5	12.5	25	65
Gender	0.5	0.5	0	1
Marital status	0.5	0.5	0	1
Education	12.5	2.5	9	16
Income	3500	1500	1000	8000
Health status	0.5	0.5	0	1
Exercise frequency	0.5	0.5	0	1
Stress level	0.5	0.5	0	1
Sleep quality	0.5	0.5	0	1
Work satisfaction	0.5	0.5	0	1
Life satisfaction	0.5	0.5	0	1

Variable	Mean	SD	Min	Max
Age	38.5	12.5	25	65
Gender	0.5	0.5	0	1
Marital status	0.5	0.5	0	1
Education	12.5	2.5	9	16
Income	3500	1500	1000	8000
Health status	0.5	0.5	0	1
Exercise frequency	0.5	0.5	0	1
Stress level	0.5	0.5	0	1
Sleep quality	0.5	0.5	0	1
Work satisfaction	0.5	0.5	0	1
Life satisfaction	0.5	0.5	0	1

Variable	Mean	SD	Min	Max
Age	38.5	12.5	25	65
Gender	0.5	0.5	0	1
Marital status	0.5	0.5	0	1
Education	12.5	2.5	9	16
Income	3500	1500	1000	8000
Health status	0.5	0.5	0	1
Exercise frequency	0.5	0.5	0	1
Stress level	0.5	0.5	0	1
Sleep quality	0.5	0.5	0	1
Work satisfaction	0.5	0.5	0	1
Life satisfaction	0.5	0.5	0	1

Variable	Mean	SD	Min	Max
Age	38.5	12.5	25	65
Gender	0.5	0.5	0	1
Marital status	0.5	0.5	0	1
Education	12.5	2.5	9	16
Income	3500	1500	1000	8000
Health status	0.5	0.5	0	1
Exercise frequency	0.5	0.5	0	1
Stress level	0.5	0.5	0	1
Sleep quality	0.5	0.5	0	1
Work satisfaction	0.5	0.5	0	1
Life satisfaction	0.5	0.5	0	1

Variable	Mean	SD	Min	Max
Age	38.5	12.5	25	65
Gender	0.5	0.5	0	1
Marital status	0.5	0.5	0	1
Education	12.5	2.5	9	16
Income	3500	1500	1000	8000
Health status	0.5	0.5	0	1
Exercise frequency	0.5	0.5	0	1
Stress level	0.5	0.5	0	1
Sleep quality	0.5	0.5	0	1
Work satisfaction	0.5	0.5	0	1
Life satisfaction	0.5	0.5	0	1

Table D-47

Example 67

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide

R ₃₂		R ₃₃		R'			
Ac		Me		CONH ₂			
Reaction 5							
Compound I-fl:mg	Ac ₂ O ml	DMAP mg	pyridine ml	Reaction time hr	Column sol.	Product	Amount mg
451	3	42.9	5	15	EA:H 1:1	I-h1	306
¹ H-NMR(CDCl ₃):δ 0.13, 0.60 and 0.87(total 6H,d,J=6.3-6.6Hz), 1.23, 1.26, 1.32 and 1.36(total 18H,s), 2.06-2.30(3H,m), 2.15, 2.16 and 2.31(total 6H,s), 2.48(1H,dd,J=7.9,13.2Hz), 2.74-2.94(2H,m), 3.05 and 3.07(total 3H,s), 3.28-3.42(2H,m), 3.88-4.00(1H,m), 4.88(1H,d,J=8.6Hz), 5.08-5.42(3H,m), 6.31(1H,brs), 6.92(2H,d,J=8.2Hz), 6.98(2H,d,J=8.2Hz), 7.08-7.26(3H,m)							
Reaction 6							
Compound I-h1:mg	NaOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg	
412	1	4	1	EA:H 1:1	I-i1	341	
¹ H-NMR(CDCl ₃):δ 0.05, 0.11, 0.52 and 0.61(total 6H,d,J=6.3-6.9Hz), 1.36, 1.37 and 1.42(total 18H,s), 1.70 and 2.05(total 3H,s), 2.00-2.42(2H,m), 2.80-3.40(5H,m), 3.04 and 3.07(total 3H,s), 3.64-3.88(1H,m), 4.76-5.32(5H,m), 5.92(1H,brs), 6.56(1H,d,J=8.2Hz), 6.88-7.30(6H,m)							

Table D-48

Example 67(Continued from Table D-47)

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-methyl-3-methylbutanamide

Reaction 7						
Compound I-11 mg	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount mg	HPLC min
330	3	2	0.5	CH:M 10:1	210	23.4
¹ H-NMR(CDCl ₃): δ 0.31, 0.69, 0.81 and 0.86(total 6H,d,J=6.3-7.0Hz), 1.38(9H,s), 1.78-1.86(1H,m), 1.85(3H,s), 2.5-2.94(3H,m), 3.05 and 3.07(total 3H,s), 3.04-3.30(1H,m), 3.50-3.84(2H,m), 4.10 and 4.40(total 1H,brs), 4.63 and 4.66(total 1H,brs), 5.06(1H,d,J=10.2Hz), 5.16-5.32(2H,m), 6.54 and 6.65(total 1H,d,J=7.9-8.2Hz), 6.80 and 6.93(total 1H,dd,J=1.5-2.0,7.9-8.2Hz), 6.98-7.14(5H,m)						

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Table D-49

Example 68

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-ethyl-3-methylbutanamide

R ₃₂		R ₃₃		R'				
H		Et		CONH ₂				
Reaction 1								
Compound T7:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.01	1.25	1.27	1.23	10	19	EA:H 1:1	I-d2	0.75
¹ H-NMR(CDCl ₃):δ 0.72,0.87, 0.92 and 0.95(total 6H,d,J=6.6-6.9Hz), 1.14-1.30(3H,m), 1.37 and 1.38(total 9H,s), 1.86-1.98(1H,m), 2.76(1/4H,dd,J=6.6,13.8Hz), 3.12(3/4H,dd,J=7.9,13.9Hz), 3.24-3.56(3H,m), 4.20 and 4.33(total 1H,dd,J=6.6-8.6,8.9Hz), 4.60 and 4.71(total 1H,t,J=7.2-7.6Hz), 5.02-5.28(7/2H,m), 5.36(1H,d,J=8.6Hz), 6.26(1/2H,brs), 6.54 and 6.58(total 1H,d,J=7.9-8.2Hz), 6.84-6.92(total 1H,m), 7.08(1H,d,J=1.7Hz), 7.20-7.40(5H,m)								
Reaction 2								Crude Compound I-e2 was used in Reaction 3.
Compound I-d2:g	Pd-C g	MeOH ml	Reaction time hr					
0.62	0.10	12	1					

Table D-50

Example 68(Continued from Table D-49)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-carbamoylethyl)-N-ethyl-3-methylbutanamide

Reaction 3								
Compound I-e2	Compound d P5:mg	NaBH ₃ CN mg	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg
Crude compound of Reaction 2	400	124	0.4	10	1	EA:H 1:1	I-f2	298
¹ H-NMR(CDCl ₃):δ 0.65, 0.87, 0.90 and 1.02(total 6H,d,J=6.2-6.9Hz), 1.12 and 1.24(total 3H,t,J=6.9-7.3Hz), 1.35, 1.37, 1.38 and 1.41(total 18H,s), 1.50-1.82(3H,m), 2.58-3.64(7H,m), 4.28-4.54(1H,m), 5.04-5.36(2H,m), 6.20-6.32 and 6.52-6.64(2H,m), 6.80-7.12(6H,m)								
Reaction 7								
Compound I-f2 mg	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
331	2	3	0.5	MC:M 20:1	234	19.7		
EI-MS(M ⁺):514								
¹ H-NMR(CDCl ₃):δ 0.56, 0.75, 0.94 and 0.96(total 6H,d,J=6.6-6.9Hz), 1.17 and 1.26(total 3H,t,J=6.9-7.3Hz), 1.38(9H,s), 1.50-1.80(2H,m), 1.98(1H,dd,J=8.6,11.2Hz), 2.20-2.50(2H,m), 2.71(1H,dd,J=3.8,13.2Hz), 2.88-3.50(5H,m), 4.54-4.62 and 4.94-5.02(1H,m), 5.21 and 6.40(total 1H,brs), 6.58(1H,d,J=8.2Hz), 6.82-7.18(6H,m)								

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Table D-51

Example 69

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-

5 hydroxyphenyl)-1-hydrozymethylethyl)-3-methylbutanamide

R ₃₂		R ₃₃		R'				
H		H		CH ₂ OH				
Reaction 1								
Compound T19:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.2	1.62	1.65	1.8	50	1.5	EA:H 1:1	I-d3	2.2
¹ H-NMR(CDCl ₃):δ 0.81(3H,brd,J=6.3Hz), 0.91(3H,d,J=6.6Hz), 1.38(9H,s), 2.0-2.2(1H,m), 2.49(1H,brs), 2.6-2.9(2H,m), 3.5-3.7(2H,m), 3.92(1H,dd,J=5.,7.9Hz), 5.11(2H,s), 5.1-5.3(2H,m), 6.09(1H,brd,J=7.6Hz), 6.57(1H,d,J=7.9Hz), 6.86(1H,dd,J=1.3,7.9Hz), 7.04(1H,d,J=1.3Hz), 7.36(5H,s)								
Reaction 2								
Compound I-d3 g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g		
2.2	0.2	48	12	Not purified	I-e3	1.6		
¹ H-NMR(CDCl ₃): δ 0.57(3H,d,J=6.6Hz), 0.89(3H,d,J=6.9Hz), 1.38(9H,s), 2.1-2.3(1H,m), 2.68(1H,dd,J=8.9,13.9Hz), 2.86(1H,dd,J=6.3,13.9Hz), 3.23(1H,d,J=3.6Hz), 3.62(1H,dd,J=6.3,10.9Hz), 3.75(1H,dd,J=3.6,10.9Hz), 4.0-4.2(1H,m), 5.45(1H,brs), 6.61(1H,d,J=7.9Hz), 6.90(1H,dd,J=2.0,7.9Hz), 7.05(1H,d,J=2.0Hz), 7.56(1H,brd,J=6.6Hz)								

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Table D-52

Example 69(Continued from Table D-51)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-

5 hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide

Reaction 3								
Compound I-e3:g	Compound P5:g	NaBH ₃ CN g	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
0.8	0.8	0.33	0.28	25	1.5	CH:M:N 300:10:1	I-f3	1.05
¹ H-NMR(CDCl ₃):δ 0.69(3H,brd,J=5.9Hz), 0.81(3H,d,J=6.9Hz), 1.38(9H,s), 1.42(9H,s), 1.8-2.0(1H,m), 2.35-3.0(6H,m), 3.0-3.2(1H,m), 3.5-3.9(3H,m), 4.1-4.3(1H,m), 4.5-4.7(1H,m), 5.47(1H,brs), 6.62(1H,d,J=7.9Hz), 6.9-7.2(6H,m), 7.36(1H,brd,J=7.6Hz)								

Reaction 7						
Compound I-f3:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount g	HPLC min
0.3	0.5	5	10	CH:M:N 200:10:1	0.21	17.7
¹ H-NMR(CDCl ₃):0.72(3H,d,J=6.9Hz), 0.83(3H,d,J=6.9Hz), 1.38(9H,s), 1.8-2.0(1H,m), 2.4-2.9(7H,m), 2.9-3.1(1H,m), 3.50(1H,dd,J=4.6,11.6Hz), 3.66(1H,dd,J=3.0,11.6Hz), 4.1-4.3(1H,m), 6.60(1H,d,J=7.9Hz), 6.92(1H,dd,J=1.7,7.9Hz), 7.0-7.2(6H,m), 7.35(1H,brd,J=8.3Hz)						

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Table D-53

Example 70

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-hydroxymethylethyl)-3-methylbutanamide

5

R ₃₂		R ₃₃		R'				
Me		H		CH ₂ OH				
Reaction 4								
Compound I-f3:g	HCHO ml	NaBH ₃ CN g	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount g
0.34	0.23	0.077	0.07	6	1.5	CH:M:N 300:10:1	I-g3	0.33
¹ H-NMR(CDCl ₃):δ 0.82(3H,d,J=6.3Hz), 0.94(3H,d,J=6.6Hz), 1.37(9H,s), 1.41(9H,s), 2.06(3H,s), 2.1-2.6(4H,m), 2.70(1H,dd,J=8.9,14.2Hz), 2.8-3.0(2H,m), 3.5-3.8(3H,m), 4.2-4.5(2H,m), 5.62(1H,brs), 6.4-6.6(1H,m), 6.62(1H,d,J=7.9Hz), 6.9-7.2(6H,m)								
Reaction 7								
Compound I-g3:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount g	HPLC min		
0.3	0.5	5	10	CH:M:N 200:10:1	0.17	20.1		
EI-MS(M ⁺):487								
¹ H-NMR(CDCl ₃):0.79(3H,d,J=6.6Hz), 0.94(3H,d,J=6.6Hz), 1.39(9H,s), 1.9-2.2(1H,m), 2.22(3H,s), 2.2-2.4(3H,m), 2.51(1H,d,J=8.9Hz), 2.6-2.8(2H,m), 2.87(1H,dd,J=6.6,14.2Hz), 3.0-3.2(1H,m), 3.57(1H,dd,J=5.3,10.9Hz), 3.72(1H,dd,J=3.6,10.9Hz), 4.1-4.3(1H,m), 6.19(1H,brd,J=7.3Hz), 6.63(1H,d,J=7.9Hz), 6.89(1H,dd,J=1.7,7.9Hz), 6.98(2H,t,J=8.6Hz), 7.0-7.2(3H,m)								

FOUO " 61206860

Table D-54

Example 71

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-

5 hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide

R ₃₂		R ₃₃		R'				
H		Me		Me				
Reaction 1								
Compound T20:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column sol.	Product	Amount g
1.62	2.22	2.25	2.46	36	16	EA:H 1:1	I-d4	2.74
¹ H-NMR (CDCl ₃): δ 0.67, 0.72, 0.89 and 0.95 (total 6H, d, J=6.6-6.9Hz), 1.08 and 1.20 (total 3H, d, J=6.6-6.9Hz), 1.37 and 1.39 (total 9H, s), 1.88-2.02 (1H, m), 2.60-2.90 (2H, m), 2.89 (3H, d, J=3.3Hz), 4.30-4.46 (1H, m), 4.90-5.00 (1H, m), 5.07 (2H, s), 6.48 and 6.59 (total 1H, d, J=7.9Hz), 6.78-6.88 (1H, m), 7.00-7.08 (1H, m), 7.30-7.40 (5H, m)								
Reaction 2								
Compound I-d4:g	Pd-C g	MeOH ml	Reaction time hr	Column sol.	Product	Amount g		
2.68	0.25	50	18	MC:M 20:1	I-e4	1.35		
¹ H-NMR (CDCl ₃): δ 0.68, 0.85, 0.95 and 0.99 (total 6H, d, J=6.6-6.9Hz), 1.11 and 1.24 (total 3H, d, J=6.6Hz), 1.88-2.04 (1H, m), 2.58-2.70 (2H, m), 2.83 and 2.91 (total 3H, s), 3.56-3.64 (1H, m), 3.95 and 4.99 (total 1H, ddd, J=6.6, 6.9, 7.6Hz), 6.62 and 6.67 (total 1H, d, J=7.9Hz), 6.77 and 6.88 (total 1H, dd, J=1.7, 7.9Hz), 6.98 and 7.02 (total 1H, d, J=1.7Hz)								

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Table D-56

Example 72

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide

R ₃₂		R ₃₃		R'				
Me		Me		Me				
Reaction 4								
Compound I -f4:g	HCHO ml	NaBH ₃ CN mg	AcOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg
520	0.39	120	0.105	9	0.5	H:EA 2:1	I-g4	404
¹ H-NMR(CDCl ₃): δ 0.28, 0.74, 0.81 and 0.91(total 6H,d,J=6.3-6.6Hz), 1.17 and 1.21(total 3H,d,J=6.6-6.9Hz), 1.37 and 1.39(total 18H,s), 1.50-1.60(1H,m), 1.58(3H,s), 1.80-2.52(4H,m), 2.60-3.14(3H,m), 2.71(3H,s), 3.62-3.78(1H,m), 4.42-4.54(1H,m), 5.32-5.44(1H,m), 6.50-7.12(8H,m)								
Reaction 7								
Compound I-g4:mg	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column sol.	Amount mg	HPLC min		
386	2	4	0.5	CH:M 10:1	272	24.5		
FAB-MS:486(M+H ⁺)								
¹ H-NMR(CDCl ₃): δ 0.44, 0.79, 0.93 and 0.96(total 6H,d,J=6.6-6.9Hz), 1.13 and 1.20(total 3H,d,J=6.6-6.9Hz), 1.39 and 1.41(total 9H,s), 1.50-1.98(3H,m), 2.04-2.18(1H,m), 2.13 and 2.30(total 3H,s), 2.32-3.10(5H,m), 2.80 and 2.86(total 3H,s), 4.18-4.28 and 5.24-5.36(total 1H,m), 6.57 and 6.61(total 1H,d,J=7.9Hz), 6.72-7.18(6H,m)								

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Table D-57

Example 73

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-

5 hydroxyphenyl)-1-methylethyl)-N-methyl-3-methylbutanamide

R ₃₂		R ₃₃		R'			
Ac		Me		Me			
Reaction 5							
Compound I-f4:mg	Ac ₂ O ml	DMAP mg	pyridine ml	Reaction time hr	Column sol.	Product	Amount mg
735	4	158	6	16.5	EA:H 1:2	I-h4	489
¹ H-NMR(CDCl ₃):δ 0.13, 0.54, 0.58 and 0.86(total 6H,d,J=6.3-6.6Hz), 1.13 and 1.15(total 3H,d,J=6.3Hz), 1.30, 1.33, 1.36 and 1.42(total 18H,s), 1.69, 2.08, 2.13 and 2.31(total 6H,s), 2.02-2.84(5H,m), 2.91 and 2.96(total 3H,s), 3.14-3.40(2H,m), 3.82-4.04(1H,m), 4.70-5.28(2H,m), 6.88-7.30(7H,m)							
Reaction 6							
Compound I-h4:mg	NaOH ml	MeOH ml	Reaction time hr	Column sol.	Product	Amount mg	
470	1	6	1	Not purified	I-i4	440	
¹ H-NMR(CDCl ₃):δ 0.11, 0.12, 0.51 and 0.64(total 6H,d,J=5.9-6.6Hz), 1.09 and 1.13(total 3H,d,J=6.3-6.6Hz), 1.37, 1.38, 1.40 and 1.43(total 18H,s), 1.66 and 2.03(total 3H,s), 2.00-2.44(3H,m), 2.62-2.72(2H,m), 2.68 and 2.92(total 3H,s), 2.88-3.40(2H,m), 3.72-3.88(1H,m), 4.52-5.32(2H,m), 6.52-7.34(7H,m)							

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[illegible][illegible][illegible][illegible][illegible]

Table D-59

Example 74

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide

R ₃₂		R ₃₃		R'				
H		H		Me				
Reaction 1								
Compound T21:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column. sol	Product	Amount g
3.000	4.350	4.400	6.00	80	5	H:EA:MC 5:1:1	I-d5	4.000
Reaction 2								
Compound I-d5:g	Pd(OH) ₂ : g	MeOH ml	Reaction time hr	Column. sol	Product	Amount g		
4.000	0.400	100	1	MC:Me:H 10:1:1	I-e5	1.200 and 0.500 (diastereomers)		
Reaction 3								
Compound I-e5:g	Compound P5:g	NaBH ₃ CN g	AcOH ml	MeOH ml	Reaction time hr	Column . sol	Product	Amount t g
1.200	1.100	0.490	0.30	30	2	H:EA:M C 3:2:2	I-f5	0.730
0.480	0.628	0.207	0.3	10	2	H:EA 1:1		0.620

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Table D-60

Example 74(Continued from Table D-59)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-

5 hydroxyphenyl)-1-methylethyl)-3-methylbutanamide

Reaction 7						
Compound I-f5:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column. sol	Amount g	HPLC min
0.500	2.00	2	1	MC:M:H 10:1:1	0.320	20.7
0.113	1.00	2	1	CH:M:N 300:10:1	0.063	20.4
<p>Compound of which yielded amount was 0.320 g with HPLC retention time of 20.7 min. EI-MS(M⁺):457 ¹H-NMR(CDCl₃):δ 0.73(3H, d, J=6.9Hz), 0.84(3H,d,J=6.9Hz), 1.08(3H,d, J=6.3Hz), 1.37(9H,s), 1.81~2.00(1H,m), 2.28-2.80(9H,m), 2.90-3.00(1H,m), 4.21~4.38 (1H,m), 6.68(1H,d,J=8.2Hz), 6.83~7.18(6H,m)</p> <p>Compound of which yielded amount was 0.063 g with HPLC retention time of 20.4 min. EI-MS(M⁺):457 ¹H-NMR(CDCl₃):δ 0.88 and 0.92(6H,d,J=6.9Hz), 1.14(3H,d,J=6.6Hz), 1.39(9H,s), 2.00-2.10(1H,m), 2.18-2.44(3H,m), 2.84-2.96(4H,m), 3.63-3.75(1H,m), 4.22-4.31(1H,m), 6.60(1H,d,J=6.8Hz), 6.86-7.26(6H, m)</p>						

FOUO " 61206860

Table D-61

Example 75

Synthesis of 2-((2-amino-3-(4-fluorophenyl)propyl)-
N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-
5 methylethyl)-3-methylbutanamide

R ₃₂		R ₃₃		R'	
Me		H		Me	

Reaction 4								
Compound I I-f5:g	HCHO ml	NaBH ₃ CN g	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
0.400	0.32	0.093	0.30	10	2	H:EA:MC 3:1:1	I-g5	0.300
0.500	0.38 0	0.118	0.10	9	2	H:EA:MC 2:1:1		0.320

Reaction 7						
Compound I-g5:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column. sol	Amount g	HPLC min
0.240	1.00	1	1	MC:M:H 10:1:1	0.140	23.0
0.320	2.00	4	1	CH:M:N 300:10:1	0.226	22.5

Compound of which yielded amount was 0.140 g with HPLC retention time of 23.0 min.
EI-MS(M⁺+1):472
¹H-NMR(CDCl₃) : δ 0.82(3H, d, J=6.6Hz), 0.93(3H,d,J=6.6Hz), 1.29(3H,d, J=6.3Hz), 1.38(9H,s), 2.03-2.80(11H,m), 2.20(3H,s), 3.00-3.14(1H,m), 4.33-4.40(1H,m), 5.64(1H,d,J=7.7Hz), 6.68(1H,d,J=7.9Hz), 6.87(1H,d,J=7.9Hz), 6.95-7.18(5H,m)

Compound of which yielded amount was 0.226 g with HPLC retention time of 22.5 min.
EI-MS(M⁺):471
¹H-NMR(CDCl₃): δ 0.68 and 0.95(6H, d, J=6.6Hz), 1.15(3H,d, J=6.6Hz), 1.37(9H,s), 2.01-2.17(1H,m), 2.21(3H,s), 2.32-2.49(4H,m), 2.64-2.72(3H,m), 3.08-3.10(1H,m), 4.22-4.32(1H,q,J=2.5Hz), 5.60(1H,d,J=6.8Hz), 6.65 and 6.84(2H,d,J=7.9Hz), 6.94-7.00(3H,dd,J=6.3,11.2Hz), 7.13-7.18(2H,m)

Table D-62

Example 76

Synthesis of 2-(N-acetyl-2-amino-3-(4-fluorophenyl)propylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-methylethyl)-3-methylbutanamide

R ₃₂		R ₃₃		R'			
Ac		H		Me			
Reaction 5							
Compound I-f5:g	Ac ₂ O ml	DMAP ml	pyridine ml	Reaction time hr	Column. sol	Product	Amount g
0.630	3.00	0.21	4.50	16	H:EA:MC 3:2:2	I-h5	0.560
Reaction 6							
Compound I-h5:g	NaOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g	
0.540	2.00	4.00	1	Not purified	I-i5	0.430	
Reaction 7							
Compound I-i5:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column. sol	Amount g	HPLC min	
0.430	2.00	2.00	1	MC:M:H 10:1:1	0.185	22.5	
EI-MS(M ⁺ +1):500							
¹ H-NMR(CDCl ₃) : δ 0.70(3H, d, J=5.6Hz), 0.84(3H,d, J=6.6Hz), 1.05(3H,d, J=6.6Hz), 1.37(9H,s), 1.78-1.96(2H,m), 1.90(3H,s), 2.43-2.74(4H,m), 3.07-3.32(2H,m), 3.46-3.56(1H,m), 3.59(1H,d,J=14.5Hz), 4.10-4.72(3H,m), 4.71(2H,s), 6.18-6.22(2H,br), 6.63-6.78(2H,m), 6.95-7.18(5H,m)							

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Table D-63

Example 77

Synthesis of 2-((2-amino-3-(4-fluorophenyl)propyl)-
N-methylamino)-N-(2-(3-tert-butyl-4-hydroxyphenyl)-1-
5 hydroxymethylethyl)-N,3-dimethylbutanamide

R ₃₂		R ₃₃		R'				
Me		Me		CH ₂ OH				
Reaction 1								
Compound T23:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column. sol	Product	Amount g
0.928	1.470	1.497	1.64	39	15	H:EA:M 2:3:1	I-d6	1.170
Reaction 2								
Compound I-d6:g	Pd-C g	MeOH ml	Reaction time hr		Column. sol	Product	Amount g	
1.170	0.220	25	1		Not purified	I-e6	0.836	
Reaction 3								
CompoundI I-e6:g	Compound P5:g	NaBH ₃ CN g	AcOH ml	MeOH ml	Reactio n time hr	Column. sol	Product	Amou nt g
0.836	0.997	0.329	0.28	25	1	MC:M:H 15:1:1	I-f6	1.20 0
Reaction 4								
CompoundI I-f6:g	HCHO ml	NaBH ₃ CN g	AcOH ml	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
0.530	0.400	0.119	0.10	9	2	H:ACT 2:1:	I-g6	0.341
Reaction 7								
Compound I-g6:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr		Column. sol	Amount g	HPLC min	
0.225	2.5	3	1		CH:M:N 300:10:1	0.100	24.3	
EI-MS(M ⁺):471								
¹ H-NMR(CDCl ₃): δ 0.12, 0.79, 0.84 and 0.98(6H, d, J=6.6-6.8Hz), 1.20(9H, s), 2.02-3.00(10H, m), 2.18 and 2.58(3H, s), 2.84 and 2.87(3H, s), 3.61-3.82(3H, m), 4.01-4.11 and 4.89-4.97(1H, m), 6.52 and 6.63(2H, d, J=8.1Hz), 6.72 and 6.89(1H, d, J=7.9Hz), 6.93-7.14(4H, m)								

Example 78

Synthesis of 2-(2-amino-3-(4-fluorophenyl))-N-methylpropylamino)-N-(1-aminomethyl-2-(3-tert-butyl-4-

5 hydroxyphenyl)ethyl)-3-methylbutanamide

R_{32}	R_{33}	R'
Me	H	CH_2NH_2

Compound T22:g	Compound V4:g	CMPI g	TEA ml	THF ml	Reaction time hr	Column. sol	Product	Amount g
0.89	0.90	0.92	0.89	13	20	MC:M:N 100:3:0.1	I-d7	1.40

1H -NMR($CDCl_3$): δ 0.80(3H,d,J=6.6Hz), 0.91(3H,d,J=6.6Hz), 1.37(9H,s), 1.42(9H,s), 2.00-2.15(1H,m), 2.55-2.90(2H,m), 3.10-3.30(2H,m), 3.90-4.20(2H,m), 4.80-4.90(1H,m), 5.11(2H,brs), 5.20-5.40(1H,m), 6.35-6.50(1H,m), 6.57(1H,d,J=7.9Hz), 6.84(1H,dd, J=1.3,7.9Hz), 7.02(1H,1.3Hz), 7.36(5H,brs)

Compound I-d7:g	Pd-C g	MeOH ml	Reaction time hr	Column. sol	Product	Amount g
1.40	0.40	40	16	MC:M:N 100:5:0.1	I-e7	0.89

1H -NMR($CDCl_3$): δ 0.56(3H,d,J=6.9Hz), 0.88(3H,d,J=6.9Hz), 1.38(9H,s), 1.43(9H,s), 2.10-2.30(1H,m), 2.65-2.85(2H,m), 3.15-3.35(3H,m), 4.15-4.30(1H,m), 4.95-5.05(1H,m), 6.62(1H,d,J=7.9Hz), 6.88(1H,dd,J=2.0,7.9Hz), 7.01(1H,d,J=2.0Hz), 7.43(1H,d,J=8.3Hz)

Example 78 (Continued from Table D-64)

5 hydroxyphenyl)ethyl)-3-methylbutanamide

General		Age		Sex		Marital		Education		Occupation		Income		Health		Lifestyle		Social		Family		Environment		Genetics		Diet		Exercise		Stress		Mental		Physical		Overall	
Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value	Variable	Value
Age	25.5	Sex	Male	Marital	Single	Education	High School	Occupation	Student	Income	\$15,000	Health	Good	Lifestyle	Active	Social	Active	Family	Small	Environment	Urban	Genetics	Normal	Diet	Vegetarian	Exercise	Regular	Stress	Low	Mental	Stable	Physical	Fit	Overall	Good		
Age	25.5	Sex	Female	Marital	Married	Education	College	Occupation	Teacher	Income	\$25,000	Health	Fair	Lifestyle	Sedentary	Social	Active	Family	Large	Environment	Rural	Genetics	Normal	Diet	Meat	Exercise	Irregular	Stress	High	Mental	Unstable	Physical	Unfit	Overall	Poor		
Age	25.5	Sex	Male	Marital	Single	Education	High School	Occupation	Student	Income	\$15,000	Health	Good	Lifestyle	Active	Social	Active	Family	Small	Environment	Urban	Genetics	Normal	Diet	Vegetarian	Exercise	Regular	Stress	Low	Mental	Stable	Physical	Fit	Overall	Good		
Age	25.5	Sex	Female	Marital	Married	Education	College	Occupation	Teacher	Income	\$25,000	Health	Fair	Lifestyle	Sedentary	Social	Active	Family	Large	Environment	Rural	Genetics	Normal	Diet	Meat	Exercise	Irregular	Stress	High	Mental	Unstable	Physical	Unfit	Overall	Poor		

Table D-66

Example 78 (Continued from Table D-55)

Synthesis of 2-(2-amino-3-(4-fluorophenyl)-N-methylpropylamino)-N-(1-aminomethyl-2-(3-tert-butyl-4-hydroxyphenyl)ethyl)-3-methylbutanamide

Reaction 7						
Compound I-g7:g	TFA ml	CH ₂ Cl ₂ ml	Reaction time hr	Column. sol	Amount g	HPLC min
0.70	10	0	1	MC:M:N 100:10:1	0.46	17.7
EI-MS(M ⁺):486 ¹ H-NMR(CDCl ₃):δ 0.83(3H,d,J=6.6Hz), 0.95(3H,d,J=6.6Hz), 1.39(9H,s), 2.00-2.90(10H,m), 2.19(3H,s), 2.95-3.10(1H,m), 4.20-4.35(1H,m), 6.06(1H,d,J=8.3Hz), 6.62(1H,d,J=7.9Hz), 6.87(1H,dd,J=1.7,7.9Hz), 6.94-7.15(5H,m)						

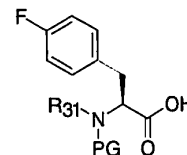
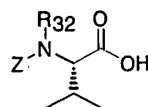
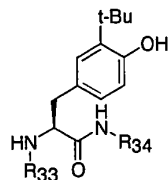
Examples 101-121 were carried out according to Scheme 3, Examples 121-131 were carried out according to Scheme 4, Example 132 was carried out according to Scheme 5, Examples 133-135 were carried out according to Scheme 6, Example 136 was carried out according to Scheme 7, Example 137 was carried out according to Scheme 8, Examples 138-165 were carried out according to Scheme 9, Examples 166 and 176 were carried out according to Scheme 10, Examples 167-171 were carried out according to Scheme 11, Examples 172 and 173 were carried out according to Scheme 12, Example 174 was carried out according to Scheme 13, Example 175 was carried out according to the scheme 14, Examples 177-179 were carried out according to Scheme 15, Example 180 was carried out according to Scheme 16, Examples 181 and 182 were carried out according to Scheme 17 and Example 183 was

Parameter	1990-1991		1991-1992		1992-1993		1993-1994		1994-1995		1995-1996		1996-1997		1997-1998		1998-1999		1999-2000		2000-2001		2001-2002		2002-2003		2003-2004		2004-2005		2005-2006		2006-2007		2007-2008		2008-2009		2009-2010		2010-2011		2011-2012		2012-2013		2013-2014		2014-2015		2015-2016		2016-2017		2017-2018		2018-2019		2019-2020		2020-2021		2021-2022		2022-2023		2023-2024		2024-2025		2025-2026		2026-2027		2027-2028		2028-2029		2029-2030		2030-2031		2031-2032		2032-2033		2033-2034		2034-2035		2035-2036		2036-2037		2037-2038		2038-2039		2039-2040		2040-2041		2041-2042		2042-2043		2043-2044		2044-2045		2045-2046		2046-2047		2047-2048		2048-2049		2049-2050		2050-2051		2051-2052		2052-2053		2053-2054		2054-2055		2055-2056		2056-2057		2057-2058		2058-2059		2059-2060		2060-2061		2061-2062		2062-2063		2063-2064		2064-2065		2065-2066		2066-2067		2067-2068		2068-2069		2069-2070		2070-2071		2071-2072		2072-2073		2073-2074		2074-2075		2075-2076		2076-2077		2077-2078		2078-2079		2079-2080		2080-2081		2081-2082		2082-2083		2083-2084		2084-2085		2085-2086		2086-2087		2087-2088		2088-2089		2089-2090		2090-2091		2091-2092		2092-2093		2093-2094		2094-2095		2095-2096		2096-2097		2097-2098		2098-2099		2099-2100		2100-2101		2101-2102		2102-2103		2103-2104		2104-2105		2105-2106		2106-2107		2107-2108		2108-2109		2109-2110		2110-2111		2111-2112		2112-2113		2113-2114		2114-2115		2115-2116		2116-2117		2117-2118		2118-2119		2119-2120		2120-2121		2121-2122		2122-2123		2123-2124		2124-2125		2125-2126		2126-2127		2127-2128		2128-2129		2129-2130		2130-2131		2131-2132		2132-2133		2133-2134		2134-2135		2135-2136		2136-2137		2137-2138		2138-2139		2139-2140		2140-2141		2141-2142		2142-2143		2143-2144		2144-2145		2145-2146		2146-2147		2147-2148		2148-2149		2149-2150		2150-2151		2151-2152		2152-2153		2153-2154		2154-2155		2155-2156		2156-2157		2157-2158		2158-2159		2159-2160		2160-2161		2161-2162		2162-2163		2163-2164		2164-2165		2165-2166		2166-2167		2167-2168		2168-2169		2169-2170		2170-2171		2171-2172		2172-2173		2173-2174		2174-2175		2175-2176		2176-2177		2177-2178		2178-2179		2179-2180		2180-2181		2181-2182		2182-2183		2183-2184		2184-2185		2185-2186		2186-2187		2187-2188		2188-2189		2189-2190		2190-2191		2191-2192		2192-2193		2193-2194		2194-2195		2195-2196		2196-2197		2197-2198		2198-2199		2199-2200		2200-2201		2201-2202		2202-2203		2203-2204		2204-2205		2205-2206		2206-2207		2207-2208		2208-2209		2209-2210		2210-2211		2211-2212		2212-2213		2213-2214		2214-2215		2215-2216		2	
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5 101-137 are shown in Table C-2.

Table C-2

Intermediates of Examples 101-137



5 T1: R33=H, R34=H

V1: R32=Me

P1: PG=Boc, R31=H

T3: R33=H, R34=Et

V2: R32=Et

P2: PG=Boc, R31=Me

T6: R33=Me, R34=Et

P3: PG=Z, R31=Et

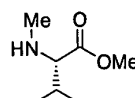
T9: R33=Et, R34=Et

P4: PG=Z, R31=H

T10: R33=H, R34=n-Pr

P5: PG=Z, R31=Me

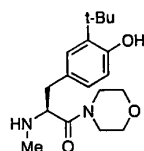
10 T11: R33=H, R34=i-Pr



V3

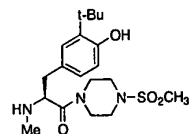
T12: R33=Me, R34=c-Pr

T16: R33=n-Pr, R34=H

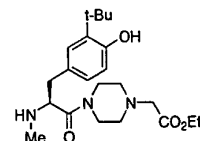


T13

15



T14



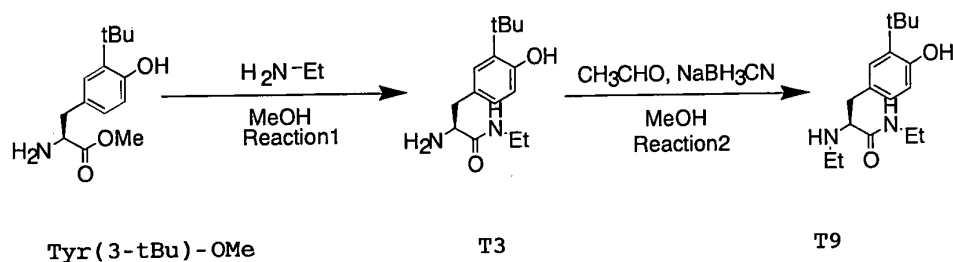
T15

Reference Example 16

Synthesis of Intermediates T3 and T9

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediates T3 and T9



The process of synthesizing Intermediates T3 and T9

10 is explained below.

Reaction step 1) Synthesis of Intermediate T3

To a solution of Tyr(3-tBu)-OMe in methanol, a 70% aqueous ethylamine solution was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, extracted with dichloromethane, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound T3.

20 Reaction step 2) Synthesis of T9

To a solution of Compound T3 and acetaldehyde in methanol, NaBH₃CN was slowly added dropwise. The reaction was stopped by the addition of an aqueous NaHCO₃ solution and the reaction mixture was concentrated under reduced pressure. The resultant was extracted with dichloromethane,

dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound T9.

- 5 The result is shown in Table E-1. In Table E-1, indications "Reaction 1" and "Reaction 2" means Reaction step 1 and Reaction step 2, "Reaction time" means stirring time, "Column sol." means the eluting solvent for silica gel column chromatography, "Product" means the obtained product and "Amount" means the yielded amount of the product. The same manner is applied to the subsequent Tables.
- 10

Table E-1

- 15 Intermediates T3 (Tyr(3-tBu)-NH₂Et) and T9 (N-Et-Tyr(3-tBu)-NH₂Et)

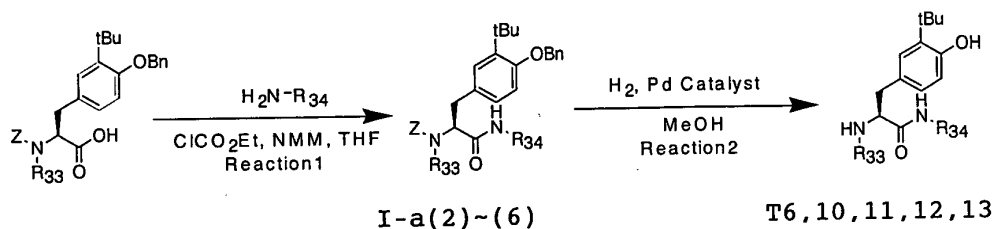
Reaction1						
Tyr(3-tBu)-OMe (g)	Ethyl amine (ml)	MeOH (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
14.000	168.00	56.00	18	nHx:EA=1:1	T3	12.810
Reaction2						
Compound T3(g)	CH ₃ CHO (ml)	NaBH ₃ CN (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
12.810	2.98	3.350	100.00	0.5	MC:MeOH =20:1	8.130

Reference Example 17

Synthesis of Intermediates T6, T10, T11, T12 and T13

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediates T6, T10, T11, T12 and T13



R_{33} and R_{34} in the above reaction scheme indicate
 10 substituents shown in Tables E-2 to E-6.

The process of synthesizing Intermediates is
 explained below.

Reaction step 1)

15 To solutions of Z-N-Me-Tyr(O-Bn, 3-tBu)-OH and ethyl
 chloroformate in THF, NMM was added. The mixture was
 stirred at room temperature and mixed with solutions of
 alkyl amines in THF. The mixtures were mixed with water,
 extracted with ethyl acetate, washed with saturated brine,
 20 dried over anhydrous magnesium and filtered. The filtrates
 were concentrated under reduced pressure and the thus
 obtained residues were subjected to silica gel column
 chromatography, giving Compounds I-a(2) to I-a(6).

Reaction step 2)

25 To solutions of Compounds I-a(2) to I-a(6) in

methanol, palladium hydroxide/carbon was added and stirred at room temperature in a hydrogen atmosphere. After filtering reaction mixtures, filtrates were concentrated under reduced pressure and the thus obtained residues were
5 subjected to silica gel column chromatography, giving Compounds T6, T10, T11, T12 and T13. The results are shown in Tables E-2 to E-6.

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Table E-2

Intermediate T6

N-Me-Tyr(3-tBu)-NH₂Et

R33					R34			
Me					Et			
Reaction 1								
Z-N-Me-Tyr(O-Bn, 3-tBu)-OH (g)	Ethylamine (ml)	ClCO ₂ Et (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
11.300	118.80	3.40	3.90	230.00	6	nHx:EA =2:1	I-a(2)	8.400
Reaction 2								
Compound I-a(2) (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)		Column sol.		Amount (g)	
6.200	0.600	120.00	3		MC:MeOH =20:1		3.600	

5

Table E-3

Intermediate T10

Tyr(3-tBu)-NH-n-Pr

R33					R34			
H					n-Pr			
Reaction 1								
Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	n-Propylamine (ml)	ClCO ₂ Et (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.100	1.40	0.57	0.66	30.00	2	nHx:EA:MC =1:3:1	I-a(3)	1.150
Reaction 2								
Compound I-a(3) (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)		Column sol.		Amount (g)	
1.150	0.200	30.00	2		MC:MeOH =20:1		0.580	

10

Table E-4

Intermediate T11

Tyr(3-tBu)-NH-i-Pr

R33				R34				
H				i-Pr				
Reaction1								
Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	i-Propyl amine (ml)	ClCO ₂ Et (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	0.72	0.54	0.46	15.00	0.6	nHx:EA=2:1	I-a(4)	1.200
Reaction2								
Compound I-a(4) (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)		Column sol.		Amount (g)	
1.200	0.500	30.00	3.5		EA:MeOH=20:1		0.660	

5

Table E-5

Intermediate T12

N-Me-Tyr(3-tBu)-NH-c-Pr

R33					R34			
Me					o-Pr			
Reaction 1								
Z-N-Me-Tyr(O-Bn,3-tBu)-CH (g)	o-Propyl-amine (ml)	ClCO ₂ Et (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.20	0.46	0.40	30.00	2	nHx:EA:MC =1:3:1	I-a(5)	1.050
Reaction 2								
Compound I-a(5) (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)		Column sol.		Amount (g)	
1.050	0.200	30.00	2		MC:MeOH =20:1		0.500	

10

Intermediate P5 was synthesized according to a similar method described in Reference Example 7.

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Table E-6

Intermediate T13

(2S)-3-[3-(tert-butyl)-4-hydroxyphenyl]-2-(methylamino)-1-morpholin-4-ylpropan-1-one

R33					R34				
Me					morpholine				
Reaction 1									
Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	morpholine (g)	ClCO ₂ Et (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
1.200	0.660	0.27	0.42	15.00	20	nHx:EA =1:1	I-a(6)	1.200	
Reaction 2									
Compound I-a(6) (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)		Column sol.		Amount (g)		
1.200	0.300	20.00	20		MC:MeOH =20:1		0.600		

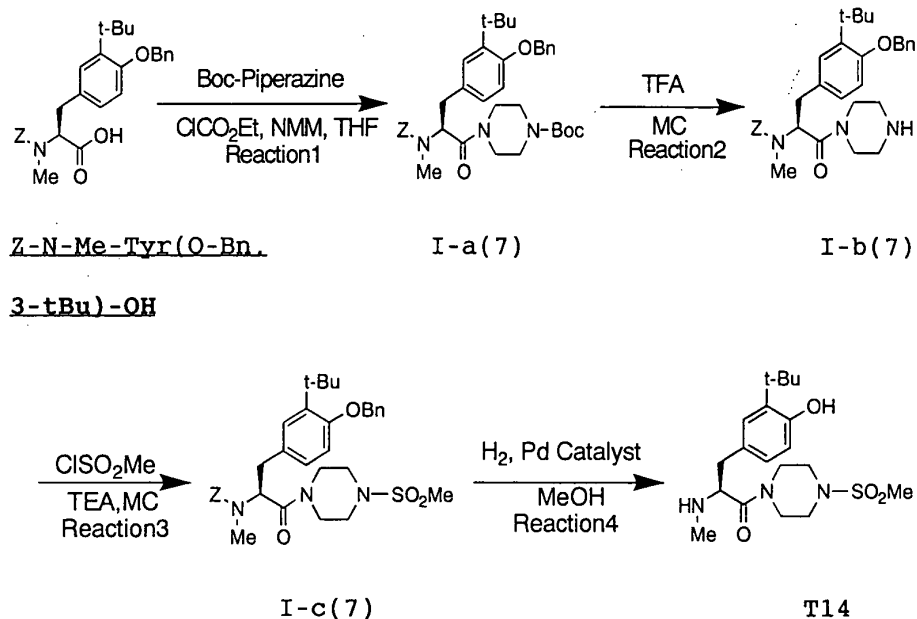
5

Reference Example 18

Synthesis of Intermediate T14

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediate T14



10

The process of synthesizing Intermediate T14 is explained below.

Reaction step 1)

15 Compound I-a(7) was obtained according to the method described in Reaction step 1 of Reference Example 17.

Reaction step 2)

To a solution of Compound I-a(7) in dichloromethane, TFA was added under cooling and stirred at room temperature.

20 The reaction mixture was concentrated under reduced pressure, extracted with dichloromethane, washed with saturated brine, dried over anhydrous magnesium sulfate and

filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound I-b(7).
Reaction step 3)

5 To a solution of Compound I-b(7) and ClSO_2Me in dichloromethane, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered.

10 The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound I-c(7).
Reaction step 4)

15 Compound T14 was obtained according to the method described in Reaction step 2 of Reference Example 17.
Result is shown in Table E-7.

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Table E-7

Intermediate T14

(2S)-3-[3-(tert-butyl)-4-hydroxyphenyl]-2-(methylamino)-1-[4-(methylsulfonyl)piperazineyl]propane-1-one

Reaction 1								
Z-N-Me-Tyr(O-Bn,3-tBu)-OH (g)	Boc-piperazine (g)	ClCO ₂ Et (ml)	NMM (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.500	0.700	0.36	0.42	15.00	20	nHx:EA=1:1	I-a(7)	1.900
Reaction 2								
Compound I-a(7) (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.900	5.00	20.00	4	MC:MeOH=20:1		I-b(7)	1.400	
Reaction 3								
Compound I-b(7) (g)	ClSO ₂ Me (ml)	TEA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
1.400	0.46	0.82	20.00	2	MC:MeOH =20:1	I-c(7)	1.500	
Reaction 4								
Compound I-c(7) (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)		Column sol.		Amount (g)	
1.500	0.300	20.00	20		MC:MeOH =20:1		0.900	

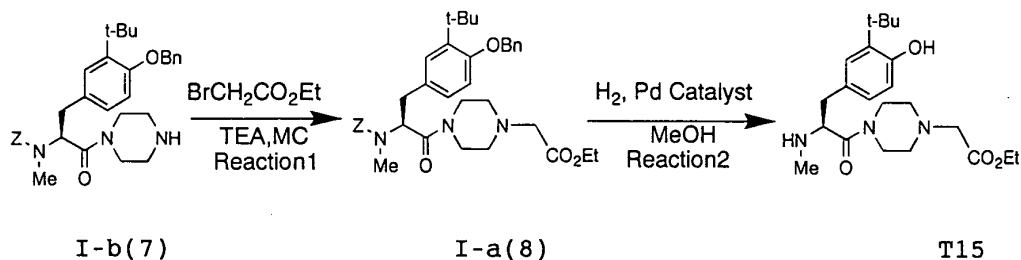
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Reference Example 19

Synthesis of Intermediate T15

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediate T15



10 The process of synthesizing Intermediate T14 is explained below.

Reaction step 1)

To a solution of Compound I-b(7) and ethyl 2-bromoacetate in dichloromethane, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound I-a(8).

Reaction step 2)

Compound T15 was obtained according to the method described in Reaction step 2 of Reference Example 17. Result is shown in Table E-8.

Table E-8

Intermediate T15

Ethyl 2-(4-((2S)-3-[3-(tert-butyl)-4-hydroxyphenyl]-2-(methylamino)propanoyl)piperazinyl)acetate

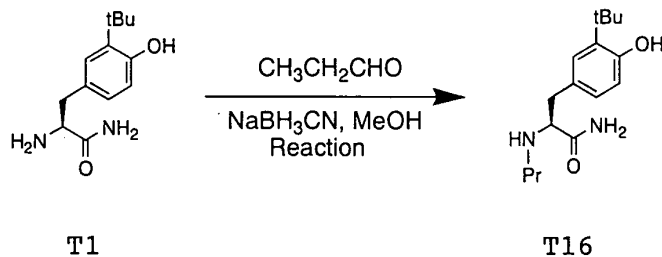
Reaction1							
Compound I-b(7) (g)	Ethyl bromo acetate(ml)	TEA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.970	0.30	0.40	17.00	4	nHex:EA=3:1	I-a(8)	1.000
Reaction2							
Compound I-a(8) (g)	Pd(OH) ₂ (g)		MeOH (ml)		Reaction time (hr)		Amount (g)
1.000	0.300		16.00		1		0.643

Reference Example 20

Synthesis of Intermediate T16

The synthesis scheme is shown below.

Synthesis scheme of Intermediate T16



The process of synthesizing Intermediate T16 is explained below.

To a solution of Compound T1 in methanol, propionaldehyde was added, stirred at room temperature for 30 min., mixed with NaBH₃CN and stirred for 2 hours. The reaction mixture was mixed with a saturated aqueous NH₄Cl solution, extracted with ethyl acetate, washed with

saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compound T16.

5 Result is shown in Table E-9.

Table E-9

Intermediate T16

N-Pr-Tyr(3-tBu)-NH₂

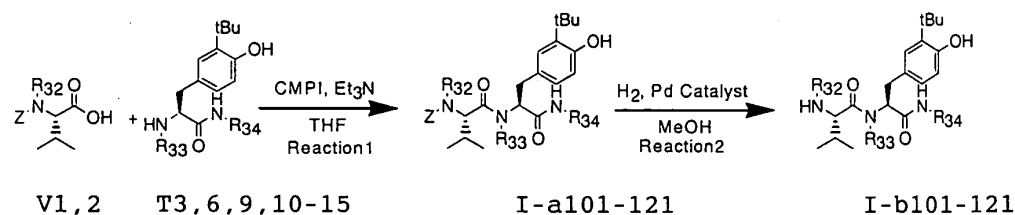
10

Reaction						
Compound T1 (g)	CH ₃ CH ₂ CHO (ml)	NaBH ₃ CN (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)
4.000	1.34	1.170	70.00	2	nHx:EA=1:2	1.580

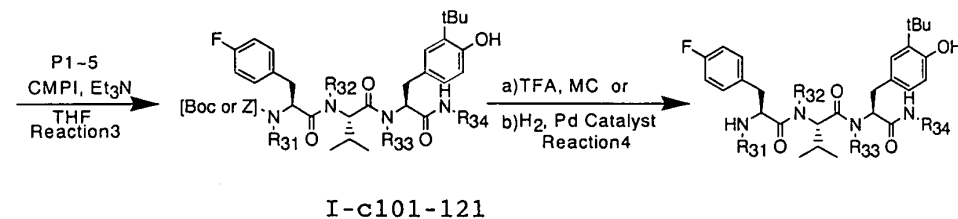
Scheme 3 shows the synthesis process of Examples 101-121.

15

Scheme 3: Synthesis process of Examples 101-121



20



R₃₁, R₃₂, R₃₃ and R₃₄ in the above reaction scheme

indicate substituents shown in Tables D-101 to D-121.

The synthesis process in scheme 3 is explained below.

Reaction step 1)

5 To solutions of Compounds T, Compounds V and CMPI in THF, TEA was added under cooling and stirred at room temperature. The mixtures were mixed with water, extracted with ethyl acetate, washed with a saturated aqueous NaHCO_3 solution, dried over anhydrous magnesium sulfate and
10 filtered. The filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-a101 to I-a121.

15 Reaction step 2)

 To solutions of Compounds I-a101 to I-a121 in methanol, Pd/C was added and stirred at room temperature in a hydrogen atmosphere. After filtering off the Pd/C, the filtrates were concentrated under reduced pressure and the
20 thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-b101 to I-b121.

Reaction step 3)

 To solutions of Compounds I-b101 to I-b121, P1 to P5
25 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered.

The filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-c101 to I-c121.

5 Reaction step 4-a)

To solutions of Compounds I-c101 to I-c121 in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixtures were neutralized by the addition of a saturated aqueous NaHCO_3 solution, extracted with dichloromethane, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving the titled compounds.

15

Reaction step 4-b)

To solutions of Compounds I-c101 to I-c121 in methanol, Pd/C or Pd(OH)_2 was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd/C or Pd(OH)_2 , the filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving the titled compounds.

Examples conducted according to Scheme 3 are shown in
25 Tables D-101 to D-121.

Table D-101

Example 101

Synthesis of Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHet

R31		R32		R33		R34		
H		Me		H		Et		
Reaction1								
Compound T3(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.000	3.000	4.350	3.30	60.00	20	nHx:EA =1:1	I-a101	5.220
Reaction2								
Compound I-a101(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
4.500	0.450	45.00	20	MC:MeOH =20:1	I-b101		2.200	
Reaction3								
Compound I-b101(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.500	0.600	0.50	15.00	20	nHx:EA =1:1	I-c101	0.830
Reaction4-b								
Compound I-c101(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.830	0.100	10.00	20	MC:MeOH =10:1		0.170	18.42	
ESI-MS(M ⁺ +1): 557								
1H-NMR(CDCI ₃): δ 0.59-1.05(9H,m), 1.37(9H, s), 2.25-2.39(1H, m), 2.58-3.24(9H, m), 3.58-3.97(2H,m), 4.44-4.62(1H,m), 5.59-5.77(1H,m), 6.60-7.72(8H,m), 9.03 and 9.06(1H, d, J=7.9Hz)								

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Table D-102

Example 102

N-Me-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NHet

R31		R32		R33		R34		
Me		Me		H		Et		
Reaction1								
Compound T3(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.000	3.000	4.350	3.30	60.00	20	nHx:EA =1:1	I-a102	5.220
Reaction2								
Compound I-a102(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
4.500	0.450	45.00	20	MC:MeOH =20:1		I-b102	2.200	
Reaction3								
Compound I-b102(g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.000	1.310	0.72	20.00	20	nHx:EA =1:1	I-c102	1.560
Reaction4-a								
Compound I-c102(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.500	1.70	10.00	4	MC:MeOH =10:1		0.28	18.73	
ESI-MS(M ⁺ +1): 557								
1H-NMR(CDCl ₃): (two rotamers) δ 0.57, 0.79, 0.92 and 1.00(9H, d and m, J=6.3-6.8Hz), 1.34and 1.38(9H, s), 2.25, 2.40 and 2.58, 2.65(6H, s), 2.05-2.40(1H, m), 2.67-3.25(6H, m), 3.55 nad 3.68(1H,m), 3.84, 4.40 and 4.55(2H, d and m, J=10.9Hz), 5.56 and 5.72(1H,m), 6.65-7.17(8H,m), 9.15 and 9.18 (1H, d, J=8.2Hz)								

Table D-103

Example 103

N-Et-Phe(4-F)-N-Me-Val -Tyr(3-tBu)-NH₂

R31		R32		R33		R34		
Et		Me		H		Et		
Reaction1								
Compound T3(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.000	3.000	4.350	3.30	60.00	20	nHx:EA =1:1	I-a103	5.220
Reaction2								
Compound I-a103(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
4.500	0.450	45.00	20	MC:MeOH =20:1		I-b103	2.200	
Reaction3								
Compound I-b103(g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.670	1.050	0.57	20.00	20	nHx:EA =1:1	I-c103	0.800
Reaction4-b								
Compound I-c103(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.800	0.100	10.00	20	MC:MeOH =10:1		0.220	19.27	
ESI-MS(M ⁺ +1): 571								
1H-NMR(CDCl ₃): (two rotamers) δ 0.42-1.20(12H,m), 1.35 and 1.39(9H, s), 2.05-2.26(1H, m), 2.31-2.54(1H, m),2.40 and 2.50(3H,s), 2.62-3.26(6H,m), 3.62-3.80(1H,m),4.34-4.58(1H,m), 5.79-5.87(1H, m), 6.60-7.04(7H, m)								

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Table D-104

Example 104

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

R31		R32		R33		R34		
H		Me		Me		Et		
Reaction1								
Compound T6 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.500	3.570	3.440	2.50	90.00	8	nHx:EA =1:2	I-a104	4.200
Reaction2								
Compound I-a104 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
4.200	0.400	75.00	5	MC:MeOH =20:1		I-b104	3.900	
Reaction3								
Compound I-b104(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.600	1.300	0.90	30.00	18	nHx:EA =1:2	I-c104	0.920
Reaction4-b								
Compound I-c104(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.920	0.100	10.00	3	MC:MeOH =20:1		0.210	19.57	
ESI-MS(M ⁺ +1): 557								
1H-NMR(CDCl ₃): (two rotamers) δ 0.56, 0.77, 0.79 and 0.92(6H, d, J=6.4-6.7Hz), 1.01-1.12(3H, m), 1.38 and 1.33(9H, s), 2.19-2.68(2H, m), 2.52 and 2.83(3H, s), 2.68-3.42(4H, m), 3.00 and 3.02(3H, s), 3.65-3.87(1H, m), 4.90-5.11 and 5.35-5.47(2H, m), 5.95-6.08(1H, m), 6.36 and 6.62(1H, d, J=7.8-7.9Hz), 6.68-7.16(6H, m)								

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Table D-105

Example 105

N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

R31		R32		R33		R34		
Me		Me		Me		Et		
Reaction1								
Compound T6 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.500	3.570	3.440	2.50	90.00	8	nHx:EA =1:2	I-a105	4.200
Reaction2								
Compound I-a105 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
4.200	0.400	75.00	5	MC:MeOH =20:1		I-b105	3.900	
Reaction3								
Compound I-b105 (g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.480	1.300	0.90	30.00	18	nHx:EA =1:2	I-c105	1.020
Reaction4-a								
Compound I-c105 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.020	2.30	23.00	6	MC:MeOH =20:1		0.200	20.213	
ESI-MS(M ⁺ +1): 571								
1H-NMR(CDCl ₃): (two rotamers) δ 0.63, 0.80, 0.81 and 0.92(6H, d, J=6.4-6.9Hz), 1.06(3H, t, J=7.3Hz), 1.34 and 1.39(9H, s), 2.13-2.33(1H, m), 2.22 and 2.25(3H, s), 2.53 and 2.82(3H s), 2.54(1H, s), 2.60-2.70(2H, m), 2.74-2.90(1H, m), 2.95 and 3.06(3H, s),3.45 and 3.59(1H, t, J=5-6.8Hz),5.07 and 5.15(1H, d, J=10.6-10.9Hz), 5.05 and 5.38(1H, dd, J=8.1-9.3, 6.1-6.8Hz), 6.0(1H, t, J=5.0Hz),6.40 and 6.61(1H, d, J=8.0Hz), 6.75(3H, m), 7.02-7.18(3H, m)								

Table D-106

Example 106

N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂Et

R31		R32		R33		R34		
Et		Me		Me		Et		
Reaction1								
Compound T6 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.500	3.570	3.440	2.50	90.00	8	nHx:EA =1:2	I-a106	4.200
Reaction2								
Compound I-a106 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
4.200	0.400	75.00	5	MC:MeOH= 20:1		I-b106	3.900	
Reaction3								
Compound I-b106 (g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.740	1.300	0.90	30.00	15	nHx:EA =1:2	I-c106	1.050
Reaction4-b								
Compound I-c106 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.050	0.100	14.00	3	MC:MeOH= 20:1		0.200	20.950	
ESI-MS(M ⁺ +1): 585								
1H-NMR(CDCl ₃): (two rotamers) δ 0.65, 0.79, 0.8 and 0.91(6H, d, J=6.0Hz), 0.97-1.08(6H, m),1.34 and 1.39(9H, s), 2.21-2.38(2H, m), 2.46-2.59(2H, m), 2.61-2.9(2H, m),2.5 and 2.75(3H, s),2.96 and 3.06(3H, s), 3.17-3.46(2H, m), 3.55 and 3.68(1H, t, J=7.0Hz), 5.01-5.36(2H, m), 5.97-6.0(1H, m), 6.41 and 6.59(1H, d, J=8.0Hz), 6.79-6.98(3H, m), 7.04-7.17(3H, m)								

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Example 107

Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH₂

R31		R32		R33		R34	
H		Me		Et		Et	
Reaction1							
Compound T9(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product Amount (g)
6.000	16.300	26.200	14.30	30.00	15	nHx:EA=2:1	I-a107 3.030
Reaction2							
Compound I-a107(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)
8.000	1.200	50.00	15	MC:MeOH = 10:1		I-b107	5.000
Reaction3							
Compound I-b107(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product Amount (g)
0.800	0.815	0.606	0.40	30.00	18	nHx:EA=1:2	I-c107 1.040
Reaction4-b							
Compound I-c107(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min
1.047	0.156	20.00	3.5	MC:MeOH =20:1		0.252	21.09
ESI-MS(M ⁺ +1):571							
¹ H-NMR(CDCl ₃):(two rotamers) δ 0.74, 0.80 and 0.92(6H, d, J=7.0-7.9Hz), 0.97-1.20(6H, m), 1.32 and 1.36(9H, s), 2.20-3.13(5H, m), 2.74 and 3.05(3H, s), 3.15-3.35(3H, m), 3.35-3.95(3H, m), 4.92-5.10(2H, m), 6.44 and 6.73(1H, d, J=8.8Hz), 6.50(3/5H, m), 6.75(3/5H, dd, J=7.9, 1.7Hz), 6.90-7.29(29/5H, m)							

Table D-108

Example 108

N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH₂

R31		R32		R33		R34		
Me		Me		Et		Et		
Reaction1								
Compound T9(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	16.300	26.200	14.30	30.00	15	nHx:EA=2:1	I-a108	3.030
Reaction2								
Compound I-a108(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
8.000	1.200	50.00	15.00	MC:MeOH = 10:1		I-b108	5.000	
Reaction3								
Compound I-b108(g)	Compound P2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.022	1.130	0.966	0.70	20.00	19	nHx:EA=1:2	I-c108	1.590
Reaction4-a								
Compound I-c108(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.590	1.80	10.00	3	MC:MeOH =20:1		0.251	21.54	
ESI-MS(M ⁺ +1):585								
1H-NMR(CDC1 ₃):(two rotamers) δ 0.78-0.90 and 0.95(6H, m and d, J=7.9Hz), 0.97-1.10(3H, m), 1.10 and 1.22(3H, m),1.31 and 1.39(9H, s), 2.21-2.25(3H, s), 2.19-2.40(1H, m),2.55-3.35(7H, m), 2.69 and 2.72(3H, s), 3.42-3.75(3H, m),4.95-5.10(1H, m),5.12(1H, d, J=10.6Hz),6.44 and 6.58(1H, d, J=8.8Hz), 6.50(3/5H,m), 6.79(3/5H, dd, J=8.1, 2.5Hz), 6.88-7.00(12/5H, m), 7.05-7.20(12/5H, m) 7.27(1H, brs)								

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Table D-109

Example 109

N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NH₂

R31		R32		R33		R34		
Et		Me		Et		Et		
Reaction1								
Compound T9(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	16.300	26.200	14.30	30.00	15	nHx:EA=2:1	I-a109	3.030
Reaction2								
Compound I-a109(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
8.000	1.200	50.00	15	MC:MeOH = 10:1		I-b109	5.000	
Reaction3								
Compound I-b109(g)	Compound P3(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.819	0.606	0.40	16.00	18	nHx:EA=1:2	I-c109	1.000
Reaction4-b								
Compound I-c109(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.000	0.150	20.00	15	MC:MeOH =20:1		0.127	21.920	
ESI-MS(M ⁺ +1):599								
1H-NMR(CDCI ₃):(two rotamers) δ 0.78-0.88 and 0.92(6H, m and d, J=7.4Hz), 0.98-1.18(6H, m), 1.20(3H, q, J=6.4Hz), 1.34 and 1.38(9H, s), 2.20-2.43(2H, m),2.43-3.35(8H, m),2.68 and 2.80(3H, s), 3.42-3.78(3H, m), 4.90-5.12(1H, m), 5.12(1H, d, J=10.6Hz), 6.42 and 6.58(1H, d, J=15.3Hz), 6.50(1/3H,m), 6.80(2/3H, dd, J=8.8, 2.1Hz), 6.85-7.00(3H, m),7.05-7.17(10/3H, m),7.30(2/3H, brs)								

Table D-110

Example 110

Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH₂

R31		R32		R33		R34		
H		Et		H		Et		
Reaction1								
Compound T3 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	6.240	8.700	6.60	120.00	20	nHx:EA=1:1	I-a110	9.540
Reaction2								
Compound I-a110 (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
6.000	0.600	60.00	20	MC:MeOH =20:1		I-b110	3.570	
Reaction3								
Compound I-b110(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.200	1.500	2.000	1.00	20.00	20	nHx:EA =1:1	I-c110	0.400
Reaction4-a								
Compound I-c110(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.400	0.60	3.00	4	MC:MeOH =20:1		0.200	20.25	
ESI-MS(M ⁺ +1): 557								
1H-NMR(CDCl ₃): δ 0.62-1.16(12H,m), 1.38(9H, s), 2.25-2.45(1H, m), 2.62-3.86(9H, m),3.92 and 3.95(1H, d, J=10.0Hz), 4.44-5.56(1H, m), 5.67-5.90(1H, m), 6.60-7.20(7H, m),9.05 and 9.08(1H, d, J=7.8Hz)								

Table D-111

Example 111

N-Me-Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH₂

R31		R32		R33		R34		
Me		Et		H		Et		
Reaction1								
Compound T3 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	6.240	8.700	6.60	120.00	20	nHx:EA =1:1	I-a111	9.540
Reaction2								
Compound I-a111 (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
6.000	0.600	60.00	20	MC:MeOH =20:1		I-b111	3.570	
Reaction3								
Compound I-b111(g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.600	2.000	1.00	20.00	20	nHx:EA =1:1	I-c111	0.400
Reaction4-a								
Compound I-c111(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.400	0.60	3.00	4	MC:MeOH =20:1		0.300	20.77	
ESI-MS(M ⁺ +1): 571								
1H-NMR(CDCl ₃): (two rotamers) δ 0.67 and 0.80-1.16(12H, d and m, J=6.8Hz), 1.37(9H, s), 2.30(3H, s), 2.35-2.39(1H, m), 2.79-3.22(8H, m), 3.53-3.59(1H, m), 4.04-4.15(1H, m), 4.39-4.46(1H, m), 5.73-5.77(1H, m), 6.61 and 6.64(1H, d, J=8.2Hz), 6.84-7.19(6H, m)								

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 "6T20680"

Table D-112

Example 112

N-Et -Phe(4-F)-N-Et-Val-Tyr(3-tBu)-NH₂

R31		R32		R33		R34		
Et		Et		H		Et		
Reaction1								
Compound T3 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
6.000	6.240	8.700	6.60	120.00	20	nHx:EA =1:1	I-a112	9.540
Reaction2								
Compound I-a112 (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
6.200	0.600	60.00	20	MC:MeOH =20:1		I-b112	3.570	
Reaction3								
Compound I-b112(g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.585	2.000	1.00	20.00	20	nHx:EA =1:1	I-c112	0.550
Reaction4-b								
Compound I-c112(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.400	0.050	4.00	20	MC:MeOH =30:1		0.098	21.090	
ESI-MS(M ⁺ +1): 585								
1H-NMR(CDCl ₃): (two rotamers) δ 0.48 and 0.71-1.31(15H, d and m, J=7.4Hz), 1.37(9H, s), 2.20-2.61(2H, m), 2.71-3.34(10H, m), 3.60-3.82(2H, m), 4.40-4.56(1H, m), 5.80-5.98(1H, m), 6.67-7.01(3H, m), 7.02-7.16(3H, m), 7.48 and 7.50(1H, d, J=6.8Hz), 8.73 and 8.76(1H,d, J=7.9Hz)								

Table D-113

Example 113

Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH₂

R31		R32		R33		R34		
H		Et		Me		Et		
Reaction1								
Compound T6 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.170	8.720	5.880	4.20	150.00	20	nHx:EA =1:2	I-a113	5.500
Reaction2								
Compound I-a113 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
5.500	0.500	100.00	2	MC:MeOH =20:1		I-b113	3.200	
Reaction3								
Compound I-b113 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.850	0.760	0.60	20.00	18	nHx:EA =1:2	I-c113	0.320
Reaction4-a								
Compound I-c113 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.320	0.70	7.40	6	MC:MeOH =20:1		0.020	20.260	
ESI-MS(M ⁺ +1): 571								
1H-NMR(CDCl ₃): (two rotamers) δ 0.36-0.96(8H,m), 0.98-1.10(4H,m), 1.35 and 1.39(9H,s), 2.28-2.41(1H,m), 2.84 and 3.04(3H,s), 2.55-3.39(8H,m), 3.68-3.78(1H,m), 4.90-5.32(2H,m) 6.45 and 6.65(1H, d, J=6.0Hz), 6.77-7.23(6H,m)								

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Table D-114

Example 114

N-Me-Phe(4-F)-N-Et-Val-N-Me-Tyr(3-tBu)-NH₂

R31		R32		R33		R34		
Me		Et		Me		Et		
Reaction1								
CompoundT6 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.170	8.720	5.880	4.20	150.00	20	nHx:EA =1:2	I-a114	5.500
Reaction2								
Compound I-a114 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
5.500	0.500	100.00	2	MC:MeOH =20:1		I-b114	3.200	
Reaction3								
Compound I-b114 (g)	Compound P2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.850	0.760	0.60	20.00	20	nHx:EA =1:2	I-c114	0.300
Reaction4-a								
Compound I-c114 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.300	0.70	6.80	6	MC:MeOH =20:1		0.030	20.880	
ESI-MS(M ⁺ +1): 585								
1H-NMR(CDCl ₃): (two rotamers) δ 0.51, 0.81, 0.87 and 0.91(6H, d, J=6.3-6.9Hz), 0.94, 1.04 and 1.17(6H, t, J=3.6Hz), 1.34 and 1.39(9H,s), 2.18-2.62(1H, m), 2.38(3H, s), 2.57-2.88 (3H,m), 2.91-3.38(5H,m), 2.94 and 3.06(3H,s), 3.49 and 3.57(1H, t, J=6.4-7.2Hz), 5.49-5.32 (2H,m), 6.02-6.1 and 6.53-6.59(1H, m), 6.45 and 6.64(1H, d, J=8.0Hz),6.76-7.03(3H, m),7.08 -7.19(3H, m)								

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T03T21_6T205360

Table D-115

Example 115

N-Et-Phe(4-F)-N-Et-Val-Me-Tyr(3-tBu)-NH₂Et

R31		R32		R33		R34		
Et		Et		Me		Et		
Reaction1								
Compound T6 (g)	Compound V2 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
4.170	8.720	5.880	4.20	150.00	20	nHx:EA =1:2	I-a115	5.500
Reaction2								
Compound I-a115 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
5.500	0.500	100.00	2	MC:MeOH =20:1		I-b115	3.200	
Reaction3								
Compound I-b115 (g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.850	0.760	0.60	20.00	18	nHx:EA =1:2	I-c115	0.300
Reaction4-b								
Compound (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.300	0.030	4.00	3	MC:MeOH =20:1		0.040	21.59	
ESI-MS(M ⁺ +1): 599								
1H-NMR(CDCl ₃):(two rotamers) δ 0.38-1.17(15H,m), 1.34, 1.36 and 1.38(9H,s), 3.38-2.12 (1H,m), 3.55(1H, t, J=6.3Hz), 3.47-3.72(1H, m), 4.88-5.37(2H, m), 5.79-6.09 and 6.63-6.7(1H, m), 6.42 and 6.62(1H, dd, J=8.3,7.4Hz), 7.05-7.22(6H,m)								

T02T2T " 6T206860

Table D-116

Example 116

Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH₂

R31		R32		R33		R34		
H		Et		Et		Et		
Reaction1								
Compound T9(g)	Compound V2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
5.020	9.110	17.550	9.50	100.00	16	nHx:EA=3:1	I-a116	3.030
Reaction2								
Compound I-a116(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
3.030	0.454	60.00	14	MC:MeOH = 10:1		I-b116	2.24	
Reaction3								
Compound I-b116(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.680	0.549	0.40	12.00	18	nHx:EA=1:1	I-c116	0.200
Reaction4-b								
Compound I-c116(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.200	0.030	4.00	3	MC:MeOH =20:1		0.053	21.59	
ESI-MS(M ⁺ +1):585								
1H-NMR(CDCl ₃):(two rotamers) δ 0.60 and 0.78-1.30(15H, d and m, J=7.9Hz), 1.34 and 1.38(9H, s), 2.22-2.50(1H, m), 2.52-3.00(3H, m), 3.00-3.54(6H, m), 3.54-3.94(2H, m), 4.82-5.05(1H, m), 5.10(1H, m), 6.45-6.70(2H, m), 6.80(3/4H, m), 6.91-7.25(21/4H, m).								

T02T2T 5T206860

Table D-117

Example 117

N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH₂t

R1		R2		R3		R4		
Me		Et		Et		Et		
Reaction1								
Compound T9(g)	Compound V2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
5.020	9.110	17.550	9.50	100.00	16	nHx:EA=3:1	I-a117	3.030
Reaction2								
Compound I-a117(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
3.030	0.454	60.00	14	M C:MeOH = 10:1		I-b117	2.240	
Reaction3								
Compound I-b117(g)	Compound P2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.845	0.681	0.585	0.40	16.00	48	nHx:EA=1:1	I-c117	0.378
Reaction4-a								
Compound I-c117(g)	TFA (ml)	M C (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.378	0.80	4.00	3	M C:MeOH = 20:1		0.056	22.20	
ESI-MS(M ⁺ +1):599								
1H-NMR(CDCl ₃):(two rotamers) δ 0.75 and 0.83-1.10(10H, d and m, J=7.9Hz), 1.10-1.30(5H, m), 1.35 and 1.39(9H, s), 2.30 and 2.33(3H, s), 2.30-2.48(1H, m), 2.65-3.89(12H, m), 4.90 and 5.07(1H, m), 5.18 and 5.23(1H, d, J=9.7Hz), 6.48 and 6.58(1H, d, J=8.8Hz), 6.63(1/2H, m), 6.80(1H, dd, J= 8.1, 1.8Hz), 6.90-7.0(7/2H, m), 7.05(1/2H, d, J=1.7Hz), 7.06-7.20(5/2H, m)								

T02T01 6T06060

Table D-118

Example 118

N-Et-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NH₂t

R31		R32		R33		R34		
Et		Et		Et		Et		
Reaction1								
Compound T9(g)	Compound V2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
5.020	9.110	17.550	9.50	100.0	16	nHx:EA=3:1	I-a118	3.030
Reaction2								
Compound I-a118(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
3.030	0.454	60.00	14	MC:MeOH = 10:1		I-b118	2.240	
Reaction3								
Compound I-b118(g)	Compound P3(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.520	0.642	0.475	0.30	10.00	48	nHx:EA=1:1	I-c118	0.174
Reaction4-b								
Compound I-c118(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.174	0.026	4.00	3	MC:MeOH =20:1		0.141	22.84	
ESI-MS(M ⁺ +1):613								
1H-NMR(CDCl ₃):(two rotamers) δ 0.75 and 0.80-0.98(8H, d and m, J=7.9Hz), 0.98-1.08(6H, m), 1.08-1.23(4H, m), 1.34 and 1.38(9H, s), 2.23-2.88(6H, m), 2.93-3.88(9H, m), 4.92 and 5.08(1H, m), 5.15 and 5.22(1H, d, J=9.7Hz), 6.49 and 6.57(1H, d, J=8.8Hz), 6.63(1/2H, m), 6.80(1/2H, dd, J=8.1, 1.7Hz), 6.85-7.00(3H, m), 7.05(1/2H, d, J=1.7Hz), 7.08-7.20(5/2H, m)								

T02221-6T306960

Table D-119

Example 119

Phe(4-F)-N-Me-Val-Tyr(3-t Bu)-NH-n-Pr

R31		R32		R33		R34		
H		Me		H		n-Pr		
Reaction1								
Compound T10(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.580	0.640	0.670	0.92	10.00	18	nHx:EA=1:1	I-a119	1.030
Reaction2								
Compound I-a119(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.030	0.200	10.00	2	MC:MeOH=15:1		I-b119	0.76	
Reaction3								
Compound I-b119(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.760	0.660	0.650	1.07	10.00	19	nHx:EA=1:2	I-c119	1.100
Reaction4-a								
Compound I-c119(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.100	6.66	13.30	2	MC:MeOH =15:1		0.210	20.10	
ESI-MS(M ⁺ +1):557								
1H-NMR(CDCl ₃): (two rotamers) δ 0.68-0.92(9H, m), 1.38 and 1.39(9H, s), 2.69 and 2.85 (3H, s), 1.37-3.20(7H, m), 3.62-3.90(1H, m), 3.93(1H, d, J=10.9Hz), 4.42-4.57(1H, m), 6.62-7.17(7H, m)								

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Table D-120

Example 120

Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NH-i-Pr

R31		R32		R33		R34		
H		Me		H		i-Pr		
Reaction1								
Compound T11 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.660	0.630	0.910	0.66	10.00	3	nHx:EA= 1:1	I-a120	1.210
Reaction2								
Compound I-a120 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.210	0.500	20.00	2	MC:MeOH =20:1		I-b120	0.900	
Reaction3								
Compound I-b120 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.900	0.650	0.880	0.64	15.00	3	nHx:EA =2:1	I-c120	1.300
Reaction4-a								
Compound I-c120 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.300	5.00	20.00	2	MC:MeOH = 25:1		0.960	19.99	
ESI-MS(M ⁺ +1):557								
1H-NMR(CDCl ₃) : (two rotamers) δ 0.70-1.07(12H, m), 1.35 and 1.38(9H, s), 1.72(2H, brs), 2.29-2.37(1H, m), 2.72 and 2.83(3H, s), 2.52-2.74(4H, m), 3.60 and 3.81(1H, dd, J=8.2 , 3.0Hz), 3.85-3.98(2H, m), 4.42-4.60(1H, m), 5.48 and 5.69(1H, d, J=7.8Hz), 6.62-6.80(2H, m), 6.90-6.98(3H, m), 7.06-7.11(2H, m), 9.07(1H, d, J=8.2Hz)								

Table D-121

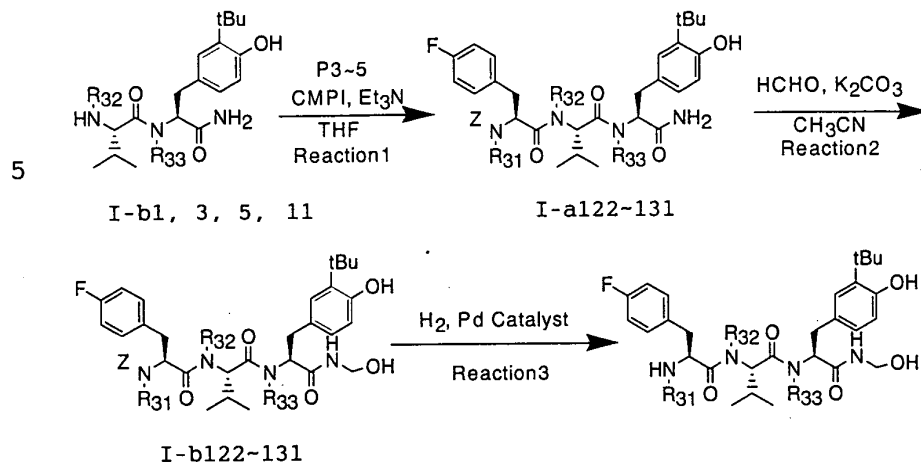
Example 121

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-t Bu)-NH-c-Pr

R31		R32		R33		R34		
H		Me		Me		c-Pr		
Reaction1								
Compound T12(g)	Compound V1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.520	0.600	0.70	10.00	18	nHx:EA:MC =1:1:1	I-a121	0.850
Reaction2								
Compound I-a121(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.850	0.200	10.00	2	MC:MeOH=15:1		I-b121	0.400	
Reaction3								
Compound I-b121(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.400	0.540	0.550	0.57	10.00	19	nHx:EA:MC =1:3:1	I-c121	0.720
Reaction4-a								
Compound I-c121(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.700	3.30	6.60	2	MC:MeOH =15:1		0.210	18.12	
ESI-MS(M ⁺ +1):569								
1H-NMR(CDC1 ₃): (two rotamers) δ 0.17-0.88(11H, m), 1.31 and 1.34(9H, s), 2.28, 2.63, 2.90 and 3.93(6H, s), 2.11-3.08 (6H, m), 4.43-5.26(3H, m), 6.48 and 6.61(1H, d, J=7.9Hz), 6.62-7.16(6H, m)								

Scheme 4 shows the synthesis process of Examples 122-131

Scheme 4: Synthesis process of Examples 122-131



10 R_{31} , R_{32} , and R_{33} in the above reaction scheme indicate substituents shown in Tables D-122 to D-131.

The synthesis process in scheme 4 is explained below.

Reaction step 1)

15 To solutions of Compounds I-b1, I-b3, I-b5 and I-b11, Compounds P3 to P5 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous

20 magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving Compounds I-a122 to I-a131.

Reaction step 2)

To solutions of Compounds I-a122 to I-a131 in CH_3CN , 38% HCHO and an aqueous K_2CO_3 solution were added and stirred at room temperature. The reaction mixtures were mixed with a saturated aqueous NH_4Cl solution, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure and the thus obtained residue was subjected to silica gel column chromatography, giving Compounds I-b122 to I-b131.

Reaction step 3)

To solutions of Compounds I-b122 to I-b131 in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd/C , the filtrates were concentrated under reduced pressure and the thus obtained residues were subjected to silica gel column chromatography, giving the titled compounds.

Examples conducted according to Scheme 4 are shown in Tables D-122 to D-131.

Table D-122

Example 122

Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH₂OH

R31			R32			R33		
H			Me			H		
Reaction1								
Compound I-b1 (g)	CompoundIP4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	0.760	0.610	0.56	40.00	4	nHc:EA=2:1	I-a122	1.000
Reaction2								
Compound I-a122(g)	HCHO (ml)	K ₂ CO ₃ (g)	CH ₃ CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
1.000	1.15	0.430	30.00	2	nHc:EA:MC =1:3:1	I-b122	0.900	
Reaction3								
Compound I-b122(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.900	0.140	13.00	2	EA:MeOH=15:1		0.560	15.91	
ESI-MS(M ⁺ +1):545								
1H-NMR(CDC ₃) ₂ (two rotamers) δ 0.69, 0.75, 0.83 and 0.90(6H, d, J=6.4-6.7Hz), 1.34 and 1.35(9H, s), 2.22-3.17(5H, m) 2.68 and 2.88(3H, s), 3.57 and 3.82(1H, dd, J=8.0-8.5, 5.5-6.0Hz), 4.51-4.74(3H, m), 6.61-9.02(8H, m)								

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Table D-123

Example 123

N-Me-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH₂OH

R31			R32			R33		
Me			Me			H		
Reaction1								
Compound I-b1 (g)	Compound P5(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.569	0.439	0.60	20.00	16	nHx:EA =1:1	I-a123	0.920
Reaction2								
Compound I-a123(g)	HCHO (ml)	K ₂ CO ₃ (g)	CH ₃ CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.910	1.00	0.380	25.00	2	nHx:EA =1:1	I-b123	0.927	
Reaction3								
Compound I-b123(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.270	0.100	10.00	1.5	EA:MeOH=30:1		0.228	16.04	
ESI-MS(M ⁺ +1):559								
1H-NMR(CDCl ₃):(two rotamers) δ 0.52, 0.77 and 0.89(6H, d, J=6.5-6.8Hz), 1.31 and 1.37(9H, s), 2.08-2.17(1H, m), 2.24 and 2.28(3H, s), 2.46 and 2.56(3H, s), 2.58-3.06(4H, m), 3.54-4.35(2H, m), 6.62-7.34(7H, m)								

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Table D-124

Example 124

N-Et-Phe(4-F)-N-Me-Val-Tyr(3-tBu)-NHCH₂OH

R31				R32		R33		
Et				Me		H		
Reaction1								
Compound I-b1 (g)	Compound P3(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.630	0.750	0.555	0.75	20.00	26	nHcEA=1:1	I-a124	0.987
Reaction2								
Compound I-a124(g)	HCHO (ml)	K ₂ CO ₃ (g)	CH ₃ CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.980	1.10	0.400	25.00	2	nHcEA=1:1	I-b124	0.911	
Reaction3								
Compound I-b124(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.910	0.200	15.00	3	MC:MeOH=15:1		0.250	16.36	
ESI-MS(M ⁺ +1):573								
1H-NMR(CDCl ₃):(two rotamers) δ 0.50, 0.75, 0.82 and 0.85(6H, d, J=6.3-7.0Hz), 0.98 and 1.12(3H, t, J=6.7Hz), 1.40 and 1.45(9H, s), 2.15(1H, m), 2.42 and 2.46(3H, s),2.40(2H, m), 2.60-3.10(5H, m),3.63(1H, dd, J=10.6, 6.0Hz), 4.50(1H, m), 4.70(2H, m), 6.70(4H, m), 6.90(1H, m), 7.00(1H, s), 7.12(1H, s), 7.20 and 7.40(1H, m), 8.75(1H, d, J=6.6Hz)								

Table D-125

Example 125

N-Me-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH₂OH

R31			R32			R33		
Me			Me			Me		
Reaction 1								
Compound I-b3(g)	Compound P5 (g)	OMPI (g)	TEA (mL)	THF (mL)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.200	1.420	1.100	0.92	30.00	14	nHk:EA:MC =1:2:1	I-a125	1.800
Reaction 2								
Compound I-a125(g)	HCHO (mL)	K ₂ CO ₃ (g)	CH ₃ CN (mL)	Reaction time (hr)	Column sol.	Product	Amount (g)	
1.790	1.970	0.730	52.00	2	nHk:EA:MC =1:3:1	I-b125	1.500	
Reaction 3								
Compound I-b125(g)	Pd/C (g)	MeOH (mL)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
1.500	0.230	20.00	2	EA:MeOH=10:1	0.970	17.27		
ESI-MS(M ⁺ +1):573								
1H-NMR(CDCl ₃):(two rotamers) d 0.57, 0.79 and 0.92(6H, d, J=6.3-6.8Hz), 1.34 and 1.38(9H, s), 2.22 and 2.25(3H, s), 2.29(1H, m), 2.52 and 2.82(3H, s), 2.55-2.89(3H, m), 2.92 and 3.04(3H, s), 3.20 and 3.39(1H, dd, J=11.1-14.1, 6.3-7.3Hz), 3.46 and 3.61(1H, t, J=6.8-6.9Hz), 4.59-4.76(2H, m), 5.03 and 5.14(1H, d, J=10.5Hz), 5.11 and 5.37(1H, dd, J=6.3, 9.7Hz), 6.39 and 6.61(1H, d, J=7.9-8.2 Hz), 6.77-7.12(6H, m)								

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Table D-126

Example 126

N-Et-Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH₂OH

R31			R32			R33		
Et			Me			Me		
Reaction1								
Compound I-b3(g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.400	1.720	1.270	1.07	38.00	14	nHx:EA =2:1	I-a126	2.110
Reaction2								
Compound I-a126(g)	HCHO (ml)	K ₂ CO ₃ (g)	CH ₃ CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
2.050	2.20	0.820	59.00	2	nHx:EA:MC =1:3:1	I-b126	2.000	
Reaction3								
Compound I-b126(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
1.950	0.290	27.00	2	EA:MeOH =10:1	1.350	18.09		
ESI-MS(M ⁺ +1):587								
1H-NMR(CDCl ₃):(two rotamers) δ 0.60, 0.79 and 0.91(6H, d, J=6.4-6.5Hz), 1.00 and 1.04(t, 3H, J=6.7-7.2Hz), 1.34 and 1.39(9H, s), 2.18-2.89(7H, m) 2.52 and 2.77(3H, s), 2.95 and 3.04(3H, s), 3.22 and 3.39(1H, dd, J=14.0-15.0, 7.9-7.6Hz),3.57 and 3.70(t, 1H, J=6.8, 6.9Hz), 4.59-4.73(2H, m),5.05 and 5.13(1H, d, J=10.6-10.7Hz), 5.13 and 5.31(1H, dd, J=9.0,7.3Hz), 6.45 and 6.62(1H, d, J=7.9 and 8.04Hz), 6.78-7.12(6H, m)								

Table D-127

Example 127

Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH₂OH

R31			R32			R33		
H			Me			Et		
Reaction1								
Compound I-b5 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.760	1.240	0.990	0.91	20.00	12	nHx:EA =1:1	I-a127	0.440
Reaction2								
Compound I-a127(g)	HCHO (ml)	K ₂ CO ₃ (g)	CH ₃ CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.420	0.76	0.035	5.00	12	nHx:EA =1:1	I-b127	0.370	
Reaction3								
Compound I-b127(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.350	0.050	15.00	3	MC:MeOH =20:1	0.100	18.26		
ESI-MS(M ⁺ +1):573								
1H-NMR(CDCl ₃) : (two rotamers) δ 0.67, 0.81 and 0.91(6H, d, J=5.9-6.9Hz),1.07 and 1.16(3H, t, J=6.8 and 6.1Hz), 1.33 and 1.38(9H, s), 2.24-2.49(2H, m) 2.58-2.75(1H, m), 2.78 and 3.05(3H, s),2.83-3.03(1H, m), 3.15-3.30(1H, m), 3.37-3.44(1H, m), 3.55-3.65(1H, m), 3.75-3.90(1H, m), 4.55-4.76(2H, m),4.85-5.06(2H, m), 6.43 and 6.61(1H, d, J=8.1-8.4Hz), 6.75-7.1(6H, m), 7.36 and 8.03(1H, brs)								

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Table D-128

Example 128

N-Me-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH₂OH

R31				R32		R33		
Me				Me		Et		
Reaction1								
Compound I-b5(g)	Compound P5 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	1.230	0.950	0.91	20.00	12	nHx:EA =1:1	I-a128	0.640
Reaction2								
Compound I-a128(g)	HCHO (ml)	K ₂ CO ₃ (g)	CH ₃ CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.610	1.10	0.051	3.00	12	nHx:EA =1:1	I-b128	0.560	
Reaction3								
Compound I-b128(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.540	0.080	23.00	1	MC:MeOH=20:1		0.200	18.85	
ESI-MS(M ⁺ +1):587								
1H-NMR(CDCl ₃):(two rotamers) δ 0.77, 0.83, 0.84 and 0.93(6H, d, J=6.4-6.8Hz), 1.12 and 1.18(3H, t, J=7.0-7.1Hz), 1.34 and 1.38(9H, s), 2.25(3H, s), 2.29-2.39(1H, m), 2.64-3.01(3H, m), 2.75 and 2.85(3H, s), 3.21-3.33(1H, m), 3.42-3.69(3H, m), 4.58-4.76(2H, m), 4.88-4.94 and 5.10-5.19(1H, m), 5.12(1H, dd, J=10.5, 2.6Hz), 6.50 and 6.61(1H, d, J=8.0Hz), 6.80-6.98(3H, m), 7.07-7.15(3H, m), 7.42 and 8.29(1H, t, J=6.0-6.4Hz)								

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Table D-129

Example 129

N-Et-Phe(4-F)-N-Me-Val-N-Et-Tyr(3-tBu)-NHCH₂OH

R31			R32			R33		
Et			Me			Et		
Reaction1								
Compound I-b5 (g)	Compound P3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.370	1.010	0.92	25.00	12	nHx:EA =1:1	I-a129	0.970
Reaction2								
Compound I-a129(g)	HCHO (ml)	K ₂ CO ₃ (g)	CH ₃ CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.950	1.70	0.079	6.00	12	nHx:EA =1:1	I-b129	0.790	
Reaction3								
Compound I-b129(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.780	0.120	30.00	2	MC:MeOH =20:1		0.300	19.68	
ESI-MS(M ⁺ +1):601								
1H-NMR(CDCl ₃):(two rotamers) δ 0.76, 0.82, 0.83 and 0.92(6H, d, J=6.4-6.9Hz), 1.00-1.28(6H, m), 1.34 and 1.38(9H,s), 2.25-2.43(2H, m), 2.49-2.59(1H, m), 2.65-2.97(3H, m), 2.72 and 2.79(3H, s), 3.17-3.33(1H, m), 3.41-3.76(3H, m), 4.52-4.74(2H, m), 4.85-4.90 and 5.12-5.16(1H, m), 5.09(1H, dd J=10.7, 3.5Hz), 6.48 and 6.59(1H, d, J=8.0-8.4Hz), 6.80-6.98(3H, m), 7.08-7.17(3H, m), 7.38 and 8.32(1H, t, J=5.7Hz)								

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Table D-130

Example 130

Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHCH₂OH

R31			R32			R33		
H			Et			Et		
Reaction1								
Compound I-bl1 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	1.250	1.000	0.68	25.00	30	nHx:EA =1:1	I-a130	0.200
Reaction2								
Compound I-a130(g)	HCHO (ml)	K ₂ CO ₃ (g)	CH ₃ CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.200	0.36	0.400	4.00	12	nHx:EA =1:1	I-b130	0.100	
Reaction3								
Compound I-b130(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.100	0.015	5.00	1	MC:MeOH =25:1		0.016	18.41	
ESI-MS(M ⁺ +1):587								
1H-NMR(CDCl ₃): (two rotamers) d 0.54, 0.81, 0.87 and 0.93(6H, d, J=6.0-6.8Hz), 1.12 and 1.19(6H, t, J=6.8-7.2Hz), 1.36 and 1.39(9H, s), 2.25-2.43(1H, m), 2.60-2.74(1H, m), 2.78-2.99(2H, m), 3.16-3.50(4H,m), 3.56-3.80(2H, m), 4.53-4.74(2H, m), 4.83-4.88 and 4.99-5.11(2H, m), 6.48 and 6.63(1H, d, J=7.9Hz), 6.80-6.85 and 6.96-7.18(6H, m), 7.46-7.49 and 7.58-								

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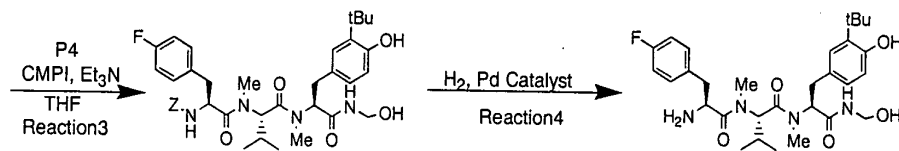
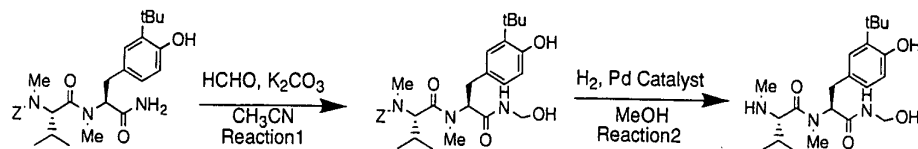
Table D-131

Example 131

N-Me-Phe(4-F)-N-Et-Val-N-Et-Tyr(3-tBu)-NHCH₂OH

R31			R32			R33		
Me			Et			Et		
Reaction1								
Compound I-b11 (g)	Compound P5 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	1.340	1.000	0.68	25.00	30	nHx:EA =1:1	I-a131	0.170
Reaction2								
Compound I-a131(g)	HCHO (ml)	K ₂ CO ₃ (g)	CH ₃ CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
0.170	0.31	0.014	4.00	12	nHx:EA =1:1	I-b131	0.080	
Reaction3								
Compound I-b131(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.080	0.012	4.00	1	MC:MeOH =25:1	0.040	18.97		
ESI-MS(M ⁺ +1):601								
1H-NMR(CDCl ₃):(two rotamers) δ 0.64(1H, d, J=6.4Hz), 0.85-0.97(7H, m), 1.10-1.19(4H, m), 1.33 and 1.37(9H, s), 2.25-2.43(1H, m), 2.29 and 2.31(3H, s), 2.67-2.86(3H, m), 3.12-3.65 and 3.74-3.81(6H, m), 4.52-4.72(2H, m), 4.87-4.92 and 5.09-5.19(2H, m), 6.45 and 6.59(1H, d, J=8.0 and 8.4Hz), 6.78(2/3H, dd, J=7.9, 1.5Hz), 6.90-6.98(7/3H, m), 7.04(2/3H, d, J=1.5Hz), 7.10-7.16(7/3H, m), 7.50 and 7.90(1H, t, J=6.3 and 6.0Hz)								

1990-1991		1991-1992		1992-1993		1993-1994		1994-1995		1995-1996		1996-1997		1997-1998		1998-1999		1999-2000		2000-2001		2001-2002		2002-2003		2003-2004		2004-2005		2005-2006		2006-2007		2007-2008		2008-2009		2009-2010		2010-2011		2011-2012		2012-2013		2013-2014		2014-2015		2015-2016		2016-2017		2017-2018		2018-2019		2019-2020		2020-2021		2021-2022		2022-2023		2023-2024		2024-2025		2025-2026		2026-2027		2027-2028		2028-2029		2029-2030		2030-2031		2031-2032		2032-2033		2033-2034		2034-2035		2035-2036		2036-2037		2037-2038		2038-2039		2039-2040		2040-2041		2041-2042		2042-2043		2043-2044		2044-2045		2045-2046		2046-2047		2047-2048		2048-2049		2049-2050		2050-2051		2051-2052		2052-2053		2053-2054		2054-2055		2055-2056		2056-2057		2057-2058		2058-2059		2059-2060		2060-2061		2061-2062		2062-2063		2063-2064		2064-2065		2065-2066		2066-2067		2067-2068		2068-2069		2069-2070		2070-2071		2071-2072		2072-2073		2073-2074		2074-2075		2075-2076		2076-2077		2077-2078		2078-2079		2079-2080		2080-2081		2081-2082		2082-2083		2083-2084		2084-2085		2085-2086		2086-2087		2087-2088		2088-2089		2089-2090		2090-2091		2091-2092		2092-2093		2093-2094		2094-2095		2095-2096		2096-2097		2097-2098		2098-2099		2099-2100		2100-2101		2101-2102		2102-2103		2103-2104		2104-2105		2105-2106		2106-2107		2107-2108		2108-2109		2109-2110		2110-2111		2111-2112		2112-2113		2113-2114		2114-2115		2115-2116		2116-2117		2117-2118		2118-2119		2119-2120		2120-2121		2121-2122		2122-2123		2123-2124		2124-2125		2125-2126		2126-2127		2127-2128		2128-2129		2129-2130		2130-2131		2131-2132		2132-2133		2133-2134		2134-2135		2135-2136		2136-2137		2137-2138		2138-2139		2139-2140		2140-2141		2141-2142		2142-2143		2143-2144		2144-2145		2145-2146		2146-2147		2147-2148		2148-2149		2149-2150		2150-2151		2151-2152		2152-2153		2153-2154		2154-2155		2155-2156		2156-2157		2157-2158		2158-2159		2159-2160		2160-2161		2161-2162		2162-2163		2163-2164		2164-2165		2165-2166		2166-2167		2167-2168		2168-2169		2169-2170		2170-2171		2171-2172		2172-2173		2173-2174		2174-2175		2175-2176		2176-2177		2177-2178		2178-2179		2179-2180		2180-2181		2181-2182		2182-2183		2183-2184		2184-2185		2185-2186		2186-2187		2187-2188		2188-2189		2189-2190		2190-2191		2191-2192		2192-2193		2193-2194		2194-2195		2195-2196		2196-2197		2197-2198		2198-2199		2199-2200		2200-2201		2201-2202		2202-2203		2203-2204		2204-2205		2205-2206		2206-2207		2207-2208		2208-2209		2209-2210		2210-2211		2211-2212		2212-2213		2213-2214		2214-2215		2215-2216		2216-2217	
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10 Reaction step 1)

 To a solution of Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ in CH₃CN, 38% HCHO and K₂CO₃ were added and stirred at room temperature. The reaction mixture was mixed with a saturated aqueous NH₄Cl solution, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a132.

Reaction step 2)

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temperature. After filtering off the Pd/C, the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-b132.

5

Reaction step 3)

To a solution of Compound I-b132, Compound P4 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-c132.

15

Reaction step 4)

To a solution of Compound I-c132 in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd/C, the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Table D-132 shows Example conducted according to Scheme 5.

Table D-132

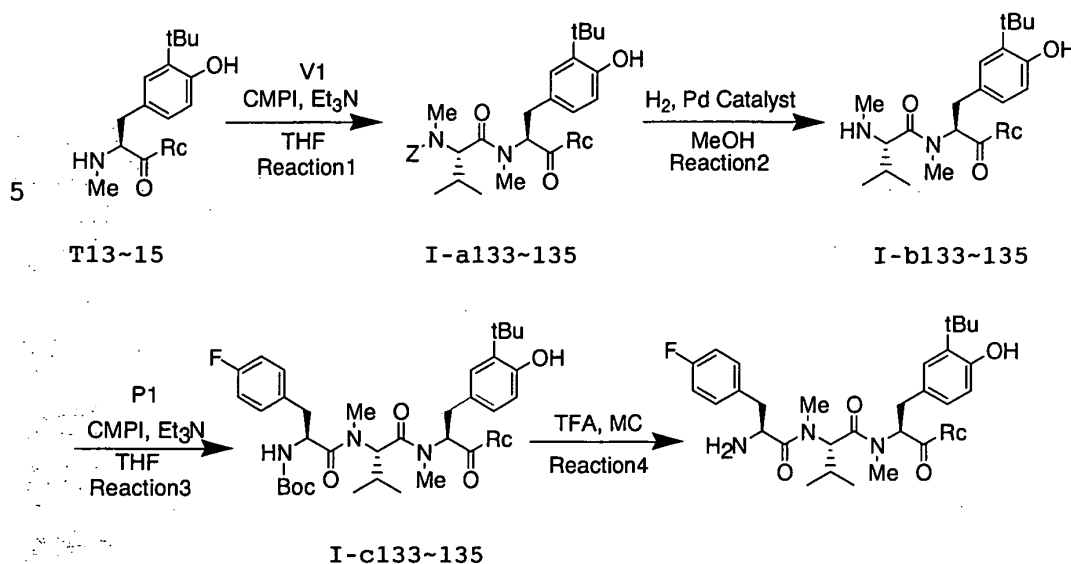
Example 132

Phe(4-F)-N-Me-Val-N-Me-Tyr(3-tBu)-NHCH₂OH

R31				R32		R33		
H				Me		Me		
Reaction1								
Z-N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂ (g)	HCHO (ml)	K ₂ CO ₃ (g)	CH ₃ CN (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
2.000	3.00	1.100	71.00	2	nHc:EA:MC=1:3:1	I-a132	2.000	
Reaction2								
Compound I-a132(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.950	0.290	50.00	1	EA:MeOH=7:1		I-b132	0.730	
Reaction3								
Compound I-b132(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.730	0.880	0.700	0.50	35.00	4	nHc:EA=1:4	I-c132	0.700
Reaction4								
Compound I-c132(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.700	0.110	10.00	4	MC:MeOH=20:1		0.410	16.64	
ESI-MS(M ⁺ +1):559								
1H-NMR(CDCl ₃): (two rotamers) δ 0.49, 0.74, 0.78 and 0.91(6H, d, J=5.9-6.6Hz), 1.33 and 1.37(9H, s), 2.20-2.97(4H, m), 2.54, 2.81 and 3.00(6H, s), 3.16 and 3.35(1H, dd, J=13.7-15.1, 6.2-6.5Hz), 3.71 and 3.85(1H, dd, J=8.1-9.4, 4.5-5.0Hz), 4.64 and 4.69(2H, d, J=6.0-6.4Hz), 4.79 and 5.06(1H, d, J=10.2-10.6Hz), 5.00 and 5.36(1H, dd, J=9.2, 5.5Hz), 6.43 and 6.64(1H, d, J=7.8Hz), 6.71-7.12(6H, m)								

Scheme 6 shows the synthesis process of Examples 133-135.

Scheme 6: Synthesis process of Examples 133-135



10 Rc in the above Scheme indicates the substituent shown in Tables D-133 to D-135.

The synthesis process in scheme 6 is explained below.
Reaction step 1)

15 To solutions of Compounds T13 to T15, Compound V1 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered.

20 The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a133 to I-

dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

- 5 Tables D-133 to D-135 show Examples conducted according to Scheme 6.

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Table D-133

Example 133

(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-((1S)-1-[[3-(tert-butyl)-4-hydroxyphenyl]methyl]-2-morpholin-4-yl-2-oxoethyl)-3-methyl-N-methylbutanamide

R								
4-morpholine								
Reaction1								
Compound T13(g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.490	0.720	0.50	20.00	20	nHx:EA = 1:1	I-a133	0.900
Reaction2								
Compound I-a133(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.900	0.100	20.00	20	MC:MeOH = 20:1		I-b133	0.600	
Reaction3								
Compound I-b133(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.450	0.530	0.40	20.00	20	nHx:EA = 1:1	I-c133	0.850
Reaction4								
Compound I-c133 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.850	3.00	10.00	4	MC:MeOH = 20:1		0.600	19.77	
ESI-MS(M ⁺ +1):599								
1H-NMR(CDC1 ₃): (two rotamers) δ 0.78 and 0.85(6H, d, J=6.2-6.7Hz), 1.37(9H, s), 2.23-2.28(1H, m), 2.24(3H, s), 2.48-2.56(1H, m), 2.79-2.87(5H, m), 3.02-3.09(1H, m), 3.40-3.74(10H, m), 5.01-5.05(1H, J=10.0 Hz), 5.79-5.84(1H,m), 6.39 and 6.41(1H,d, J=7.9Hz), 6.74-6.77(1H,m), 6.99-7.18(6H,m)								

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Table D-134

Example 134

(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-((1S)-1-[[3-(tert-butyl)-4-hydroxyphenyl]methyl]-2-[4-(methylsulfonyl)piperazinyl]-2-oxoethyl)-3-methyl-N-methylbutanamide

R								
4-(methylsulfonyl) piperazine								
Reaction1								
Compound T14(g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.200	0.790	1.100	0.84	20.00	20	nHx:EA = 1:1	I-a134	1.500
Reaction2								
Compound I-a134 (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.500	0.300	20.00	20	M C:MeOH = 20:1		I-b134	0.900	
Reaction3								
Compound I-b134 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	0.520	0.430	0.38	15	2	nHx:EA = 1:1	I-c134	0.700
Reaction4								
Compound I-c134 (g)	TFA (ml)	M C (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.700	3.00	10.00	4	M C:MeOH = 20:1		0.350	19.94	
ESI-MS(M ⁺ +1):677								
1H-NMR(CDC ₁₃): (two rotamers) δ 0.79 and 0.85(6H, d, J=6.2-6.7Hz), 1.37(9H, s), 2.23-2.28(1H, m), 2.52-2.69(4H, m), 2.73(3H, s), 2.75-2.89(7H, m), 3.01-3.16(4H, m), 3.58-3.78(1H, m), 5.03 and 5.07(1H, d, J=10.6 Hz), 5.75-5.81(1H, m), 6.42 and 6.45(1H, d, J=7.9Hz), 6.76-6.80(1H, m), 6.99-7.18(6H, m)								

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Table D-135

Example 135

Ethyl 2-[4-((2S)-2-((2S)-2-((2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-3,N-dimethylbutanoylamino)-3-[3-(tert-butyl)-4-hydroxyphenyl]propanoyl)piperazinyl]acetate

R								
ethyl-2-piperazinylacetate								
Reaction1								
Compound T15 (g)	Compound V1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.643	0.547	0.527	0.50	16.00	16	nHx:EA= 2:3	I-a135	0.827
Reaction2								
Compound I-a135 (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.827	0.250	13.00	1	MC:MeOH =20:1		I-b135	0.645	
Reaction3								
Compound I-b135 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.645	0.458	0.413	0.40	12	16	nHx:EA= 2:3	I-c135	0.796
Reaction4								
Compound I-c135(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.796	2.00	5.00	1	MC:MeOH =30:1		0.430	17.1	
ESI-MS(M ⁺ +1):684								
1H-NMR(CDCl ₃): (two rotamers) δ 0.77 and 0.84(6H, d, J=6.4-6.8Hz), 1.26(3H, t, J=7.1Hz), 1.26(9H, s), 2.22-2.30(1H, m), 2.47-2.54(1H, m), 3.00-3.07(1H, m) 2.40, 2.81 and 3.18(6H, s), 3.54-3.73(5H, m), 4.18(2H, q, J=7.1Hz), 5.03(2H, d, J=10.4Hz), 5.85(1H, t, J=2.3Hz), 6.40(1H, d, J=7.9Hz), 6.72-6.75 (1H, dd, J=9.7, 1.9Hz), 7.00-7.26(5H, m)								

[illegible]

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Table D-136

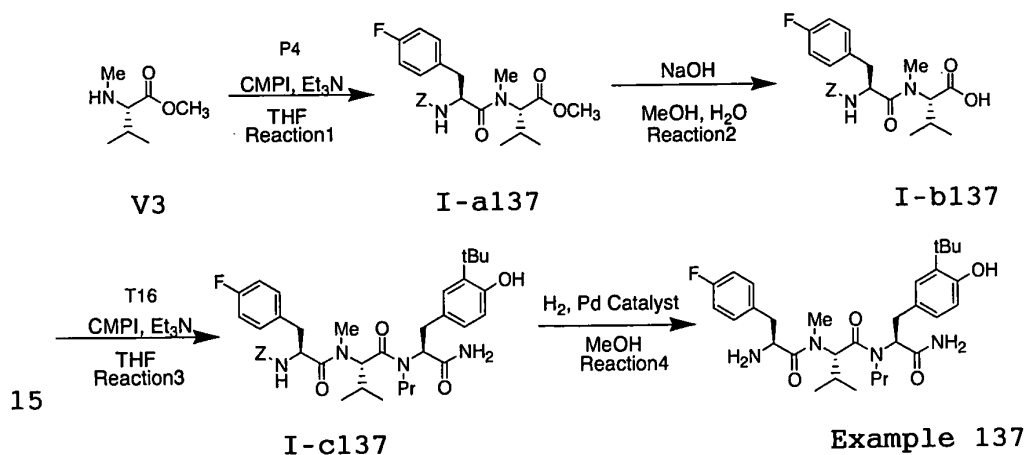
Example 136

2-[4-((2S)-2-((2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-3,N-dimethylbutanoylamino)-3-[3-(tert-butyl)-4-hydroxyphenyl]propanoyl)piperazinyl]acetic acid

Reaction							
Compound of Example 135(g)	NaOH (g)	H ₂ O (ml)	Dioxane (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.375	0.400	5.00	5.00	16	MC:MeOH=20:1	0.200	14.97
ESI-MS(M ⁺ +1):656							
¹ H-NMR(CD ₃ OD): (two rotamers) δ 0.78 and 0.82(6H, d, J=6.1Hz), 1.27(9H, s), 2.12-2.29(1H, m), 2.74-3.12(8H, m), 3.61-3.82(4H, m), 2.48, 2.94, 3.25 and 3.55(6H, s), 4.50-4.56(1H, q, J=10.5Hz), 5.02(1H, d, J=10.5Hz), 5.73(1H, t, J=7.9Hz), 6.74-6.78(1H, dd, J=9.4, 2.2Hz), 7.00-7.27(6H, m)							

Scheme 8 shows the synthesis process of Example 137.

Scheme 8: Synthesis process of Example 137



The synthesis process in scheme 8 is explained below.

Reaction step 1)

To a solution of Compound V3, Compound P4 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a137.

10 Reaction step 2)

To a solution of Compound I-a137 in methanol, NaOH and water were added and stirred at room temperature. The reaction mixture was mixed with a saturated aqueous NH_4Cl solution, concentrated under reduced pressure, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-b137.

20

Reaction step 3)

To a solution of Compound I-b137, Compound T16 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with 25 water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography

(silica gel) to give Compound I-cl37.

Reaction step 4)

To a solution of Compound 1-cl37 in methanol, Pd/C
5 was added and stirred in a hydrogen atmosphere at room
temperature. After filtering off the Pd/C, the filtrate
was concentrated under reduced pressure; the thus obtained
residue was purified by column chromatography (silica gel)
to give the titled compound.

10 Table D-137 shows Example conducted according to
Scheme 8.

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Table D-137

Example 137

Phe(4-F)-N-Me-Val-N-Pr-Tyr(3-tBu)-NH₂

Reaction1								
Compound V3 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.146	3.000	2.410	2.20	28.00	12	nHx:EA=5:1	I-a137	1.877

Reaction2						
Compound I-a137(g)	NaOH (g)	H ₂ O (ml)	MeOH (ml)	Reaction time (hr)	Product	Amount (g)
1.870	0.646	8.00	40.00	8	I-b137	1.710

Reaction3								
Compound I-b137(g)	Compound T10 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.710	0.709	0.976	0.88	14.00	12	nHx:EA=3:2	I-c137	0.610

Reaction4						
Compound I-c137(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.400	0.080	16.00	1	MC:MeOH =25:1	0.128	22.7

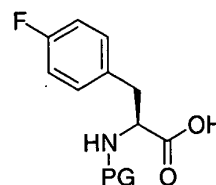
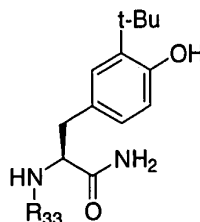
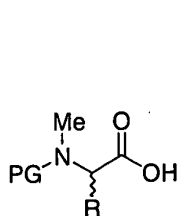
ESI-MS(M ⁺ +1):557						
1H-NMR(CDCl ₃): δ 0.66(3H, d, J=6.6Hz), 0.80(3H, d, J=6.5Hz), 0.84(3H, t, J=7.4Hz), 1.33(9H, s), 1.43-1.59(2H, m), 2.20-2.28(1H, m), 2.53(1H, dd, J=13.5, 9.1Hz), 2.60-2.75(2H, m), 2.95(1H, dd, J=13.8, 4.8Hz), 3.01(3H, s), 3.20(1H, dd, J=14.1, 6.2Hz), 3.32(1H, dd, J=13.6, 10.9Hz), 3.52-3.63(1H, m), 3.89-3.93(1H, m), 4.21-4.28(1H, m), 4.89(1H, d, J=10.6Hz), 5.48(1H, brs), 6.51(1H, d, J=7.9Hz), 6.73(1H, dd, J=7.9, 1.9Hz), 6.82(1H, brs), 6.99-7.10(3H, m), 7.11-7.16(2H, m)						

5

The processes of synthesizing Intermediates of Schemes 9-14 are shown below as Reference Examples. In addition, structural formulae of Intermediates of Examples 138-176 are shown in Tables C-3 and C-4.

Table C-3

Intermediates of Examples 138-176

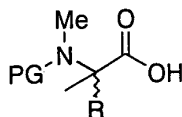


- | | | | |
|----|---|------------|-----------------|
| | I1: R=Et , I2: R=Et(D) | T1: R33=H | P1: PG=Z or Boc |
| 5 | I3: R=n-Pr, I4: R=n-Pr(D) | T4: R33=Me | P4: PG=Z or Boc |
| | I5: R=s-Bu (commercial), I6: R=s-Bu(D) | | |
| | I7: R=i-Bu (commercial), I8: R=i-Bu(D) | | |
| | I9: R=Allyl, I10: R=Allyl(L,D-mixture) | | |
| | I11: R=neo-Pentyl, I12: R=neo-Pentyl(D) | | |
| 10 | I13: R=CH ₂ CF ₃ (L,D-mixture) | | |
| | I14: R=c-Hex, I15: R=c-Hex(D) | | |
| | I16: R=CH ₂ c-Hex, I17: R=CH ₂ c-Hex(D) | | |
| | I18: R=CH ₂ Ph, I19: R=CH ₂ Ph(D) | | |
| | I20: R=CH ₂ Ph(4-F), I21: R=CH ₂ Ph(4-F)(D) | | |
| 15 | I22: R=CH ₂ Ph(4-Cl), I23: R=CH ₂ Ph(4-Cl)(D) | | |
| | I24: R=CH ₂ Ph(4-OBn), I25: R=CH ₂ Ph(4-OBn)(D) | | |
| | I26: R=CH ₂ (2-thienyl), I27: R=CH ₂ (2-thienyl)(D) | | |
| | I28: R=CH ₂ c-Pr | | |
| | I38: R=tBu | | |
| 20 | I29: N-Me-Phg-OMe, I30: N-Me-D-Phg-OMe | | |

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Table C-4

Intermediates of Examples 138-176 (continued)

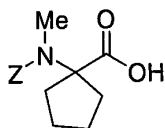


I31: R=CH₂Ph, I32: R=CH₂Ph(D)

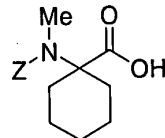
5 I33: R=i-Bu

I34: R=Et(D)

I35: R=i-Pr(D)



I36



I37

10

In Tables C-3 and C-4, "commercial" means that the compound is commercially available, "(D)" means a D-amino acid in stereochemistry and those which are not indicated as (D) are L-amino acids. PG in the Intermediate (I)

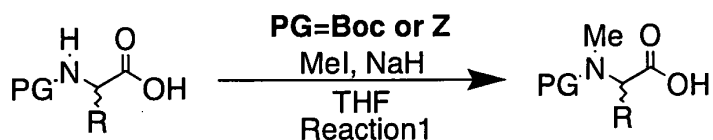
15 means Z or Boc.

Reference Example 21

Synthesis of Intermediates I1 to I28

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediates I1 to I28



Z or Boc-Amino acid

I1-28

10 The synthesis process of Intermediates I1 to I28 is explained below.

Reaction step 1)

To solutions of Z- and Boc-protected amino acids in THF, NaH and MeI were added under cooling and stirred at room temperature. The reaction mixtures were mixed with
15 water, adjusted to pH 3-4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column
20 chromatography (silica gel) to give Compounds I1 to I28.

Results are shown in Tables E-10 to E-35.

Table E-10

Intermediates I1: Z-N-Me-Abu-OH

R						
Et						
Reaction						
Z-Abu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	4.20	1.340	40.00	15	MC:MeOH =10:1	1.400

5 Table E-11

Intermediate I2: Boc-N-Me-D-Abu-OH

R						
Et:D						
Reaction						
Boc-(D)-Abu- OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.750	1.83	0.738	18.00	48	MC:MeOH =8:1	0.810

Table E-12

10 Intermediate I3: Z-N-Me-Nva-OH

R						
n-Pr						
Reaction						
Z-Nva-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	5.00	0.960	30.00	24	MC:MeOH =10:1	2.090

Table E-13

Intermediate I4: Boc-N-Me-D-Nva-OH

R						
n-Pr:D						
Reaction						
Boc-(D)-Nva-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	2.87	0.552	25.00	40	MC:MeOH =10:1	1.000

5 Table E-14

Intermediate I6: Boc-N-Me-D-Ile-OH

R						
s-Bu:D						
Reaction						
Boc-(D)-Ile-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.500	1.35	0.866	17.00	12	MC:MeOH =10:1	0.490

Table E-15

10 Intermediate I8: Boc-N-Me-D-Leu-OH

R						
i-Bu:D						
Reaction						
Boc-(D)-Leu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	2.49	1.600	17.00	12	MC:MeOH =15:1	0.960

Table E-16

Intermediate I9:

(2S)-2-[N-(tert-butoxycarbonyl)-methylamino]pent-4-enoic acid

R						
Allyl						
Reaction						
(2S)-2-[(tert-butoxy)carbonylamino]pent-4-enoic acid (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.660	1.79	1.150	12.00	12	MC:MeOH =10:1	0.570

5

Table E-17

Intermediate I10:

2-[N-(tert-butoxycarbonyl)-methylamino]pent-4-enoic acid

R						
Allyl: D,L-mixture						
Reaction						
2-[(tert-butoxy)carbonyl - amino]pent-4-enoic acid (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.656	7.67	4.924	51.00	12	MC:MeOH =15:1	2.360

Table E-18

Intermediate I11: BOC-N-Me-Leu(γ -Me)-OH

R						
neo-Pent						
Reaction						
BOC-Leu(γ -Me)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.930	4.86	3.120	40.00	48	MC:MeOH =10:1	1.500

5 Table E-19

Intermediate I12: BOC-N-Me-D-Leu(γ -Me)-OH

R						
neo-Pent:D						
Reaction						
BOC-(D)-Leu(γ -Me)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	2.50	1.630	20.00	24	MC:MeOH =10:1	1.110

Table E-20

10 Intermediate I13: 2-[N-(phenylmethoxy)carbonyl-methylamino]-4,4,4-trifluorobutanoic acid

R						
CH ₂ CF ₃ :L,D-mixture						
Reaction						
Z-2-amino-4,4,4-trifluorobutanoic acid (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.75	1.61	1.03	20.00	12	MC:MeOH =10:1	0.567

Table E-21

Intermediate I14: Boc-N-Me-Chg-OH

R						
c-Hex						
Reaction						
Boc-Chg-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.60	2.300	40.00	20	MC:MeOH =30:1	1.500

5 Table E-22

Intermediate I15: Boc-N-Me-D-Chg-OH

R						
c-Hex:D						
Reaction						
Boc-(D)-Chg-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.500	2.70	1.740	30.00	20	MC:MeOH =30:1	1.150

10 Table E-23

Intermediate I16: Boc-N-Me-Cha-OH

R						
CH ₂ c-Hex						
Reaction						
Boc-Cha-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.40	1.100	23.00	18	MC:MeOH =10:1	1.300

Table E-24

Intermediate I17: Boc-N-Me-D-Cha-OH

R						
CH ₂ c-Hex:D						
Reaction						
Boc-(D)-Cha-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.72	0.552	11.50	18	MC:MeOH =10:1	1.000

5 Table E-25

Intermediate I18: Boc-N-Me-Phe-OH

R						
CH ₂ Ph						
Reaction						
Boc-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.66	0.400	20.00	20	MC:MeOH =20:1	0.800

Table E-26

10 Intermediate I19: Boc-N-Me-D-Phe-OH

R						
CH ₂ Ph:D						
Reaction						
Boc-(D)-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
0.890	1.66	0.400	20.00	20	MC:MeOH =20:1	0.800

Table E-27

Intermediate I20: Boc-N-Me-Phe(4-F)-OH

R						
CH ₂ Phe(4-F)						
Reaction						
Boc-Phe-(4-F)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
15.000	27.00	6.360	180.00	24	MC:MeOH =10:1	15.000

5 Table E-28

Intermediate I21: Boc-N-Me-D-Phe(4-F)-OH

R						
CH ₂ Phe(4-F):D						
Reaction						
Boc-(D)-Phe(4-F)- OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.76	0.424	12.00	18	MC:MeOH =10:1	1.000

0990219 244204
 102121 51206860

Table E-29

Intermediate I22: Boc-N-Me-Phe(4-Cl)-OH

R						
CH ₂ Ph(4-Cl)						
Reaction						
Boc-Phe(4-Cl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.32	0.800	40.00	18	MC:MeOH =20:1	1.630

5 Table E-30

Intermediate I23: Boc-N-Me-D-Phe(4-Cl)-OH

R						
CH ₂ Ph(4-Cl):D						
Reaction						
Boc-(D)-Phe(4-Cl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.66	0.401	20.00	18	MC:MeOH =20:1	0.781

Table E-31

10 Intermediate I24: Boc-N-Me-Phe(4-OBn)-OH

R						
CH ₂ Ph(4-OBn)						
Reaction						
Boc-Phe(4-OBn)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.500	3.35	0.808	50.00	36	MC:MeOH =20:1	2.590

Table E-32

Intermediate I25: Z-N-Me-D-Phe(4-OBn)-OH

R						
CH ₂ Ph(4-OBn):D						
Reaction						
Z-(D)-Phe(4-OBn)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	2.51	0.592	40.00	36	MC:MeOH =20:1	2.060

Table E-33

5 Intermediate I26: Boc-N-Me-Ala(β -2-thienyl)-OH

R						
CH ₂ (2-Thienyl)						
Reaction						
Boc-Ala(beta-2-thienyl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.84	0.443	20.00	18	MC:MeOH =20:1	0.916

Table E-34

Intermediate I27: Boc-N-Me-D-Ala(β -2-thienyl)-OH

R						
CH ₂ (2-Thienyl):D						
Reaction						
Boc-(D)-Ala(beta-2-thienyl)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.000	1.84	0.443	20.00	18	MC:MeOH =20:1	1.040

Table E-35

Intermediate I28: Z-N-Me-Ala(β -c-Pr)-OH

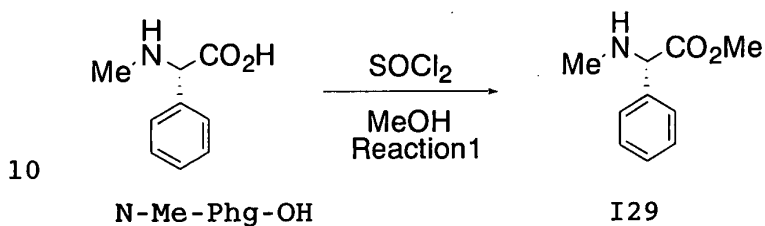
R						
CH ₂ c-Propyl						
Reaction						
Z-N-Ala(beta-c-Pr)-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.500	2.84	0.680	15.00	15	MC:MeOH =10:1	1.160

5 Reference Example 22

Synthesis of Intermediate I29

The synthesis scheme is shown below.

Synthesis scheme of Intermediate I29



The synthesis process of Intermediate I29 is explained below.

15

Reaction step 1)

To a solution of N-Me-Phg-OH in methanol, SOCl₂ was slowly added dropwise under cooling and then stirred under reflux. The reaction mixture was concentrated under reduced pressure to give crude Compound I29.

20

Result is shown in Table E-36.

Table E-36

Intermediate I29: N-Me-Phg-OMe

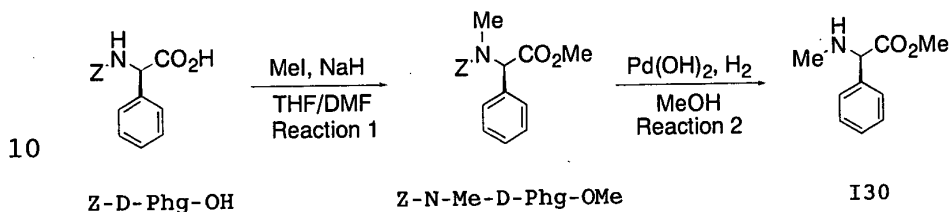
Reaction				
N-Me-Phg-OH (g)	SOCl ₂ (ml)	MeOH (ml)	Reaction time (hr)	Amount (g)
2.000	1.32	20.00	3.00	2.000

5 Reference Example 23

Synthesis of Intermediate I30

The synthesis scheme is shown below.

Synthesis scheme of Intermediate I30



The synthesis process of Intermediate I30 is explained below.

15 Reaction step 1)

To a solution of Z-D-Phg-OH and CH₃I in THF and DMF, NaH was slowly added dropwise and then stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Z-N-Me-D-Phg-OMe.

20

Reaction step 2)

To a solution of Z-N-Me-D-Phg-OMe in methanol, palladium hydroxide/carbon was added and stirred in a hydrogen atmosphere at room temperature. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel), giving Compound I30.

Result is shown in Table E-37.

Table E-37

Intermediate I30: N-Me-D-Phg-OMe

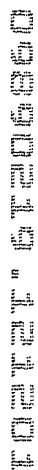
R							
Ph :D							
Reaction1							
Z-N-Me-(D)-Phg-OH (g)	Methyl iodide (ml)	NaH (g)	THF/DMF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.000	3.49	0.842	20.00 (10.00/10.00)	16	nHx:EA=5:1	Z-N-Me-(D)-Phg-OMe	2.200
Reaction2							
Z-N-Me-(D)-Phg-OMe(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)		Column sol.	Amount (g)	
2.200	0.330	40.00	12		nHx:EA=5:1	1.240	

Reference Example 24

Synthesis of Intermediates I31-I35

The synthesis scheme is shown below.

Synthesis scheme of Intermediates I31-I35



- 325 -

Reaction step 1)

To solutions of α -Me-amino acids and Na_2CO_3 in dioxane and water, Z-Cl was slowly added dropwise under cooling while stirring. The reaction mixtures were mixed with
5 water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel), giving Z- α -Me-amino acids.

10

Reaction step 2)

T solutions of the Z- α -Me-Amino acid and CH_3I in THF, NaH was slowly added dropwise under cooling. The reaction mixtures were adjusted to pH 3-4 by the addition of 1N HCl,
15 extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to giving Compounds I31 to I35.

20

Results are shown in Tables E-38 to E-42.

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Table E-38

Intermediate I31: Z-N-Me- α -Me-Phe-OH

R								
CH ₂ Ph								
Reaction1								
alpha-Me-Phe-OH (g)	Z-Cl (ml)	Na ₂ CO ₃ (g)	Dioxane (ml)	H ₂ O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.90	0.900	25.00	25.00	5	MC:MeOH =10:1	Z-alpha-Me-Phe-OH	0.890
Reaction2								
Z-alpha-Me-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.890	1.40	0.340	28.00	15	MC:MeOH =10:1		1.180	

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Table E-39

Intermediate I32: Z-N-Me- α -Me-D-Phe-OH

R								
CH ₂ Ph:D								
Reaction1								
alpha-Me-(D)-Phe-OH (g)	Z-Cl (ml)	Na ₂ CO ₃ (g)	Dioxane (ml)	H ₂ O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.90	0.900	25.00	25.00	5	MC:MeOH =10:1	Z-alpha-Me-(D)-Phe-OH	0.810
Reaction2								
Z-alpha-Me-(D)-Phe-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.810	1.40	0.340	28.00	15	MC:MeOH =10:1		1.050	

5

Table E-40

Intermediate I33: Z-N-Me- α -Me-Leu-OH

R								
i-Bu								
Reaction1								
alpha-Me-Leu-OH (g)	Z-Cl (ml)	Na ₂ CO ₃ (g)	Dioxane (ml)	H ₂ O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.970	2.10	2.140	30.00	20.00	24	MC:MeOH =10:1	Z-alpha-Me-Leu-OH	2.000
Reaction2								
Z-alpha-Me-Leu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
2.000	4.40	2.000	35.00	12	MC:MeOH =10:1		1.780	

10

TOTAL: 67206860

Table E-41

Intermediate I34: Z-N-Me- α -Me-D-Abu-OH

R								
CH ₂ CH ₃ :D								
Reaction1								
alpha-Me-(D)- Abu-OH (g)	Z-Cl (ml)	Na ₂ CO ₃ (g)	THF (ml)	H ₂ O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.250	0.36	0.450	10.00	2.00	3	MC:MeOH =10:1	Z-alpha-Me- (D)-Et-OH	0.177
Reaction2								
Z-alpha-Me- (D)-Abu-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.750	0.42	0.190	10.00	12	MC:MeOH=10:1		0.152	

5

Table E-42

Intermediate I35: Z-N-Me- α -Me-D-Val-OH

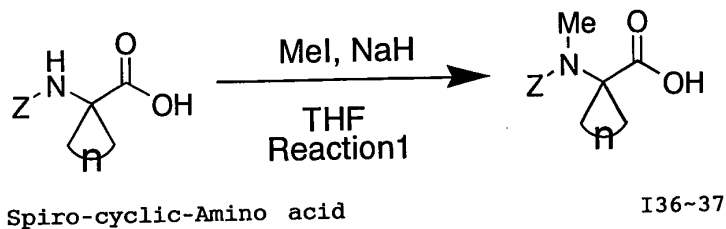
R								
i-Pr:D								
Reaction1								
alpha-Me-(D)- Val-OH (g)	Z-Cl (ml)	Na ₂ CO ₃ (g)	Dioxane (ml)	H ₂ O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.31	1.454	4.00	4.00	12	MC:MeOH =15:1	Z-alpha-Me- (D)-Val-OH	0.170
Reaction2								
Z-alpha-Me-(D)- Val-OH (g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.		Amount (g)	
0.170	0.40	0.128	3.00	12	MC:MeOH=10:1		0.170	

Reference Example 25

Synthesis of Intermediate I36, I37

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediates I36 and I37



The synthesis process of Intermediates I36 and I37 is explained below.

Reaction step 1)

To solutions of a spiro-cyclic-amino acids and CH_3I in THF, NaH was slowly added dropwise under cooling. The reaction mixtures were adjusted to pH 3-4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I36 and I37.

Results are shown in Tables E-43 and E-44.

Table E-43

Intermediate I36:

1-[N-

methyl(phenylmethoxy)carbonylamino]cyclopentanecarboxylic

5 acid

Reaction						
Z-1-amino-1-cyclopentanecarboxylic acid(g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
2.000	3.79	0.912	26.00	18	MC:MeOH =20:1	1.730

Table E-44

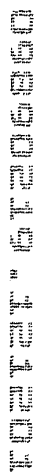
Intermediate I37:

1-[N-

10 methyl(phenylmethoxy)carbonylamino]cyclohexanecarboxylic

acid

Reaction						
Z-1-amino-1-cyclohexanecarboxylic acid(g)	Methyl iodide (ml)	NaH (g)	THF (ml)	Reaction time (hr)	Column sol.	Amount (g)
4.000	7.19	1.730	80.00	18	MC:MeOH =20:1	4.190

[illegible][illegible][illegible][illegible][illegible][illegible][illegible][illegible][illegible]

thus obtained residue was purified by column chromatography
(silica gel), giving Intermediate I38.

Result is shown in Table E-45.

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Table E-45

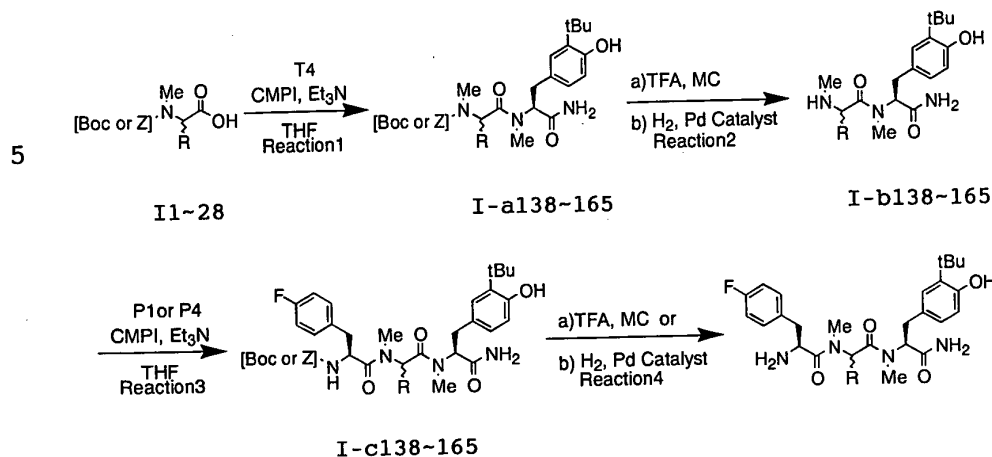
Intermediate I38: Boc-N-Me-Tle-OH

Reaction1						
Boc-Tle-OH (g)	Methyl iodide (ml)	NaH (g)	DMF (ml)	Reaction time (hr)	Product	Amount (g)
1.000	2.70	0.865	18.00	16	Boc-N-Me-Tle-OMe	1.180
Reaction2						
Boc-N-Me-Tle-OMe (g)	NaOH (g)	MeOH (ml)	H ₂ O (ml)	Reaction time (hr)	Column sol.	Amount (g)
1.180	0.550	10.00	2.00	22	MC:MeOH=10:1	0.900

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Scheme 9 shows the synthesis process of Examples 138-165.

Scheme 9: Synthesis process of Examples 138-165



10 The synthesis process in scheme 9 is explained below.

Reaction step 1)

To solutions of Compound T4, Compounds I1 to I28 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a138 to I-

15

20 a165.

Reaction step 2-a)

To solutions of Compounds I-a in dichloromethane, TFA was added under cooling and stirred at room temperature.

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The reaction mixtures were concentrated under reduced pressure, neutralized by the addition of a saturated aqueous NaHCO_3 solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The
5 filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-b.

Reaction step 2-b)

10 To solutions of Compounds I-a in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off Pd/C, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica
15 gel) to give Compounds I-b.

Reaction step 3)

To solutions of Compounds I-b138 to I-b165, Compound P1 or P4 and CMPI in THF, TEA was added under cooling and
20 stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by
25 column chromatography (silica gel) to give Compounds I-c138 to I-c165.

Reaction step 4-a)

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To solutions of Compounds I-c in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixtures were concentrated under reduced pressure, neutralized by the addition of a saturated aqueous NaHCO₃ solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

10

Reaction step 4-b)

To solutions of Compounds I-c in methanol, Pd/C was added and stirred in a hydrogen atmosphere at room temperature. After filtering off Pd/C, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

Compounds which were synthesized in Examples according to Scheme 9 are shown in Tables D-138 to D-165. In the tables "A" indicated after the Example number means "less polar isomer" and "B" means "more polar isomer". For example, Compound of Example 150A is "less polar isomer" of Phe(4-F)-N-Me-Ala(β -CF₃)-N-Me-Tyr(3-tBu)-NH₂ and Compound of Example 150B is "more polar isomer" of Phe(4-F)-N-Me-Ala(β -CF₃)-N-Me-Tyr(3-tBu)-NH₂.

Table D-138

Example 138

Phe(4-F)-N-Me-Abu-N-Me-Tyr(3-tBu)-NH₂

R								
Et								
Reaction1								
Compound T4 (g)	Compound I1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.960	0.980	0.90	30.00	12	nHx:EA=1:2	I-a138	1.420
Reaction2-b								
Compound I-a138(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
1.400	0.430	28.00	2	MC:MeOH=15:1	I-b138		0.950	
Reaction3								
Compound I-b138(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.890	0.860	0.780	0.70	5.00	72	nHx:EA=1:1	I-c138	0.720
Reaction4-a								
Compound I-c138(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
0.720	1.80	9.00	3	MC:MeOH=15:1	0.420		17.07	
ESI-MS(M ⁺ +1):515								
1H-NMR(CD ₃ OD):(two rotamers) δ 0.55 and 0.88(3H, t, J=7.2-7.6Hz), 1.39 and 1.44(9H, s), 1.56-1.85(2H, m), 2.23, 2.62, 2.91 and 2.98(6H, s), 2.56-3.01(4H, m), 3.26(1H, dt, J=3.0-4.7, 13.9-15.4Hz), 3.78 and 3.97(1H, dd, J=8.4, 5.1Hz), 5.28 and 5.55(1H, dd, J=7.8-11.6, 4.8-6.0Hz), 6.59 and 6.74(1H, d, J=8.0Hz), 6.69-7.30(6H, m)								

Table D-139

Example 139

Phe(4-F)-N-Me-D-Abu-N-Me-Tyr(3-tBu)-NH₂

R								
Et:D								
Reaction1								
Compound T4 (g)	Compound I2(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.800	0.950	0.85	60.00	12	nHx:EA =1:2	I-a139	1.100
Reaction2-a								
Compound I-a139(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
1.100	4.90	26.00	1	MC:MeOH =8:1	I-b139		0.770	
Reaction3								
Compound I-b139(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.750	0.670	0.60	44.00	72	nHx:EA =1:2	I-c139	1.310
Reaction4-a								
Compound I-c139(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
1.300	4.20	21.00	2	MC:MeOH= 15:1	0.620		19.96	
ESI-MS(M ⁺ +1):515								
1H-NMR(CD ₃ OD): δ 0.48(3H, t, J=7.5Hz), 1.36(9H, s), 1.38-1.43(2H, m), 2.59 and 2.87(3H, s), 2.73(1H, dd, J=13.2, 7.5 Hz), 2.81-2.92(2H, m), 3.02 and 3.14(3H, s), 3.37(1H, dd, J=15.0, 6.1Hz), 3.93(1H, t, J=6.8-7.1Hz), 4.82(1H, t, J=7.7Hz), 5.34(1H, brs), 5.50(1H, dd, J=11.3, 5.9Hz), 6.42(1H, brs), 6.57(1H, d, J=7.8Hz), 6.88(1H, dd, J=7.7, 2.0Hz), 6.96(2H, t, J=8.6Hz), 7.08(1H, d, J=2.3Hz), 7.13(2H, m)								

Table D-140

Example 140

Phe(4-F)-N-Me-Nva-N-Me-Tyr(3-tBu)-NH₂

R								
n-Pr								
Reaction1								
Compound T4 (g)	Compound I3 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.830	0.800	0.847	0.84	30.00	24	nHx:EA =1:2	I-a140	1.372
Reaction2-b								
Compound I-a140(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
1.372	0.200	80.00	2	MC:MeOH =10:1	I-b140		0.895	
Reaction3								
Compound I-b140(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.480	0.387	0.40	20.00	16	nHx:EA =1:2	I-c140	0.744
Reaction4-b								
Compound I-c140(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
0.727	0.200	50.00	2	MC:MeOH =10:1	0.450		19.05	
ESI-MS(M ⁺ +1):529								
1H-NMR(CDCl ₃ +CD ₃ OD): (two rotamers) δ 0.20 and 0.70-1.20(3H, m), 0.65 and 0.75(3H, t, J=6.9Hz), 1.50-1.70(1H, m), 1.33 and 1.38(9H, s), 2.30 and 2.69(3H, s), 2.47 and 2.70(2H, m), 2.72(3H,s), 2.80 and 2.92(2H, m), 3.65 and 3.85(1H,m), 4.83(1H, m), 5.84(1H, m), 6.48(1H, d, J=9.69Hz), 6.70-6.82(1H, m), 6.90-7.20(5H, m)								

Table D-141

Example 141

Phe(4-F)-N-Me-D-Nva-N-Me-Tyr(3-tBu)-NH₂

R								
n-Pr:D								
Reaction1								
Compound T4 (g)	Compound I4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.650	0.547	0.665	0.70	20.00	16	nHx:EA =1:2	I-a141	0.670
Reaction2-a								
Compound I-a141(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
0.670	1.50	10.00	2	MC:MeOH =10:1	I-b141		0.500	
Reaction3								
Compound I-b141(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.490	0.480	0.387	0.40	20.00	16	nHx:EA =1:2	I-c141	0.680
Reaction4-b								
Compound I-c141(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
0.680	0.100	20.00	2	MC:MeOH =10:1	0.358		22.27	
ESI-MS(M ⁺ +1):529								
1H-NMR(CDCl ₃ +CD ₃ OD): (two rotamers) δ 0.65-0.90(2H, m), 0.75(3H, t, J=6.9Hz), 1.20-1.50(2H, m), 1.37 and 1.39(9H, s), 2.75(2H, brs), 2.85 and 2.87(3H,s), 2.80(1H, m), 3.00 and 3.02(3H, s), 3.45(1H, m), 3.95(1H, t, J=7.2Hz), 4.91(1H, t, J=7.5Hz), 5.40(2H, m, brs), 6.40(1H, brs), 6.60(1H, d, J=9.3Hz), 6.37(1H, d, 9.3Hz), 6.90-7.18(5H, m)								

Table D-142

Example 142

Phe(4-F)-N-Me-Ile-N-Me-Tyr(3-tBu)-NH₂

R								
s-Bu								
Reaction1								
Compound T4 (g)	Compound I5 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.750	1.000	0.910	0.83	19.00	12	nHx:EA= 2:3	I-a142	1.350
Reaction2-b								
Compound I-a142 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
1.300	0.190	50.00	2	MC:MeOH =20:1	I-b142		0.920	
Reaction3								
Compound I-b142 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.920	0.830	0.750	0.67	25.00	12	nHx:EA=2:3	I-c142	1.170
Reaction4-a								
Compound I-c142 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
1.150	2.75	13.00	3	MC:MeOH =20:1	0.710		19.710	
ESI-MS(M ⁺ +1):543								
1H-NMR(CDCl ₃ + CD ₃ OD):(two rotamers) δ 0.38, 0.81, 0.85 and 0.88(6H, d, J=6.0-6.5Hz), 0.93-1.02(1H, m), 1.18-1.29(1H, m), 1.34 and 1.39(9H, s), 1.97-2.11(1H, m), 2.38-2.93(3H, m), 2.50, 2.86, 2.95 and 3.00(6H, s), 3.11-3.18(1H, m), 3.69 and 3.84(1H, dd, J=8.0-8.9, 4.0-5.5Hz), 4.91-4.96 and 5.02-5.14(4/3H, m), 5.45(2/3H, dd, J=10.2, 5.7Hz), 6.48(2/3H, d, J=7.9Hz), 6.65-6.71(1H, m), 6.91-7.12(16/3H, m)								

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Table D-143

Example 143

Phe(4-F)-N-Me-D-Ile-N-Me-Tyr(3-tBu)-NH₂

R								
s-Bu:D								
Reaction1								
Compound T4 (g)	Compound I6 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.420	0.490	0.510	0.46	10.00	12	nHx:EA =2:3	I-a143	0.330
Reaction2-a								
Compound I-a143 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Product		Amount (g)	
0.310	0.94	4.70	3	MC:MeOH = 10:1	I-b143		0.240	
Reaction3								
Compound I-b143 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.240	0.220	0.200	0.18	6.00	12	nHx:EA =2:3	I-c143	0.340
Reaction4-a								
Compound I-c143 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)		HPLC min	
0.330	1.20	6.00	4	MC:MeOH = 10:1	0.140		23.200	
ESI-MS(M ⁺ +1):543								
1H-NMR(CDCl ₃): δ 0.27(3H, d, J=6.8Hz), 0.67-0.80(4H, m), 0.88-0.97(1H, m), 1.36(9H, s), 1.74-1.85(1H, m), 2.71(1H, dd, J=13.9, 7.2Hz), 2.84-3.00(2H, m), 2.96(3H, s), 3.12(3H, s), 3.35(1H, dd, J=14.6, 5.2Hz), 3.96(1H, t, J=7.0Hz), 4.79(1H, d, J=11.0Hz), 5.46(1H, dd, J=11.5, 5.4Hz), 5.50(1H, brs), 6.35(1H, brs), 6.58(1H, d, J=8.0Hz), 6.90-7.05(4H, m), 7.12-7.16(2H, m)								

Table D-144

Example 144

Phe(4-F)-N-Me-Leu-N-Me-Tyr(3-tBu)-NH₂

R								
i-Bu								
Reaction1								
Compound T4 (g)	Compound I7 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.747	1.000	0.910	0.83	19.00	12	nHx:EA=2:3	I-a144	1.320
Reaction2-b								
Compound I-a144 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.300	0.190	50.00	2	MC:MeOH =20:1		I-b144	0.940	
Reaction3								
Compound I-b144 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.940	0.850	0.760	0.69	25.00	12	nHx:EA =2:3	I-c144	1.230
Reaction4-a								
Compound I-c144 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.210	2.90	14.50	3	MC:MeOH =20:1		0.750	19.380	
ESI-MS(M ⁺ +1):543								
1H-NMR(CD ₃ OD):(two rotamers) δ 0.66, 0.73, 0.94 and 0.96(6H, d, J=6.0-6.6Hz),1.37 and 1.40(9H, s), 1.40-1.52(2H, m), 1.55-1.68(1H, m), 2.26 and 2.65(3H, s), 2.53-2.69(1H, m), 2.69-3.00(1H, m),2.86 and 3.00(3H, s), 3.09-3.29(1H, m),3.72-3.78 and 3.90-3.94(1H, m), 4.56-4.64(1H, m),4.94-5.06(1H, m), 5.39-5.52(1H, m), 6.55-6.78(2H, m), 6.94-7.30(5H, m)								

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Example 145

Phe(4-F)-N-Me-D-Leu-N-Me-Tyr(3-tBu)-NH₂

R								
i-Bu:D								
Reaction1								
Compound T4 (g)	Compound I8 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.810	0.960	1.000	0.91	25.00	12	nHx:EA=2:3	I-a145	1.450
Reaction2-a								
Compound I-a145 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.430	4.60	23.00	3	MC:MeOH =5:1		I-b145	1.140	
Reaction3								
Compound I-b145 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.140	1.010	0.910	0.83	25.00	12	nHx:EA=2:3	I-c145	0.940
Reaction4-a								
Compound I-c145 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.920	2.20	11.00	3	MC:MeOH =5:1		0.60	21.40	
ESI-MS(M ⁺ +1):543								
¹ H-NMR(CDCl ₃): δ 0.72(3H, d, J=4.3Hz), 0.73(3H, d, J=4.1Hz), 0.81-0.92(2H, m), 1.24-1.30(1H, m), 1.36(9H, s), 2.73-2.90(3H, m), 2.84(3H, s), 2.99(3H, s), 3.30(1H, dd, J=14.6, 5.6Hz), 3.96(1H, t, J=7.2Hz), 5.02(1H, dd, J=9.9, 4.9Hz), 5.44(1H, dd, J=10.9, 5.6Hz), 5.63(1H, brs), 6.38(1H, brs), 6.57(1H, d, J=8.4Hz), 6.85(1H, dd, J=7.8, 1.9Hz), 6.91-7.01(3H, m), 7.09-7.13(2H, m)								

Table D-146

Example 146

(2S)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-N-methylpent-4-enamide

R								
Allyl								
Reaction1								
Compound T4 (g)	Compound I9 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.573	0.630	0.700	0.64	14.00	12	nHx:EA=2:3	I-a146	0.900
Reaction2-a								
Compound I-a146 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.870	2.90	14.0	3	MC:MeOH=10:1		I-b146	0.660	
Reaction3								
Compound I-b146 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.660	0.620	0.560	0.51	17.00	12	nHx:EA =2:3	I-c146	0.570
Reaction4-a								
Compound I-c146 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.550	1.35	5.40	3	MC:MeOH=10:1		0.36	17.750	
ESI-MS(M ⁺ +1):527								
1H-NMR(CDCl ₃): (two rotamers) δ 0.97-1.04(1/2H, m), 1.34 and 1.36(9H, s), 2.12-2.24(1/2H, m), 2.32-2.75(2H, m), 2.34 and 2.66(3H, s), 2.84-2.99(2H, m), 2.97(3H, s), 3.07-3.18(1H, m), 3.62-3.66 and 3.83-3.87(1H, m), 4.80-5.09(3H, m), 5.25-5.33 and 5.63-5.76(1H, m), 5.35-5.46(1H, m), 5.39(1H, brs), 6.06(0.5H, brs), 6.41 and 6.58(1H, d, J=8.2 and 8.0Hz), 6.74 and 6.83(1H, dd, J=7.9, 1.9Hz), 6.92-7.00(2H, m), 7.03-7.14(3H, m), 7.36(1/2H, brs)								

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Table D-147

Example 147

(2R)-2-[(2S)-2-amino-3-(4-fluorophenyl)-N-methylpropanoylamino]-N-[(1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl]-N-methylpent-4-enamide

R								
Allyl:D								
Reaction1								
Compound T4 (g)	Compound I10 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.180	1.300	1.440	1.30	30.00	12	nHx:EA =1:1	I-a147	0.340
Reaction2-a								
Compound I-a147 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.330	1.10	5.00	3	MC:MeOH=7:1		I-b147	0.270	
Reaction3								
Compound I-b147 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.270	0.240	0.220	0.30	6.00	12	nHx:EA =2:3	I-c147	0.370
Reaction4-a								
Compound I-c147 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.350	1.30	5.00	3	MC:MeOH=7:1		0.24	20.320	
ESI-MS(M ⁺ +1):527								
1H-NMR(CDCl ₃): δ 1.35(9H, s), 1.99-2.16(2H, m), 2.64-2.72(1H, m), 2.79-2.89(2H, m), 2.87(3H, s), 2.97(3H, s), 3.31(1H, d, J=15.3, 5.9Hz), 3.90(1H, t, J=7.0Hz), 4.87-4.93(2H, m), 5.01(1H, dd, J=9.0, 6.7Hz), 5.16-5.29(1H, m), 5.44(1H, dd, J=10.5, 6.0Hz), 5.50(1H, brs), 6.37(1H, brs), 6.57(1H, d, J=7.8Hz), 6.85(1H, dd, J=7.9, 1.9Hz), 6.92-6.98(2H, m), 7.02(1H, d, J=2.2Hz), 7.09-7.13(2H, m)								

Table D-148

Example 148

Phe(4-F)-N-Me-Leu(γ -Me)-N-Me-Tyr(3-tBu)-NH₂

R								
neo-Pent								
Reaction1								
Compound T4 (g)	Compound I11 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.630	0.780	0.770	0.35	25.00	48	nHx:EA =1:2	I-a148	0.850
Reaction2-a								
Compound I-a148(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.800	2.50	12.50	4	MC:MeOH=9:1		I-b148	0.600	
Reaction3								
Compound I-b148(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.580	0.470	0.42	30.00	12	nHx:EA:MC =1:2:1	I-c148	0.950
Reaction4-b								
Compound I-c148(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.950	0.140	13.00	3	MC:MeOH=20:1		0.58	20.96	
ESI-MS(M ⁺ +1):557								
1H-NMR(CD ₃ OD):(two rotamers) δ 0.71 and 0.99(9H, s), 1.43 and 1.46(9H, s), 1.28-1.40(2H, m), 2.43, 2.81, 2.97 and 3.07(6H, s), 2.23-3.04(4H, m), 3.25-3.28(1H, m), 3.79(2/3H, m), 3.92(1/3H, dd, J=9.8, 4.6Hz), 5.58 and 5.53(1H, dd, J=6.9-8.2, 4.8-6.9Hz), 6.61 and 6.80(1H, d, J=8.2Hz), 6.74-7.37(6H, m)								

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Table D-149

Example 149

Phe(4-F)-N-Me-D-Leu(γ -Me)-N-Me-Tyr(3-tBu)-NH₂

R								
neoPent:D								
Reaction1								
Compound T4 (g)	Compound I12 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.990	0.980	0.90	30.00	12	nHx:EA=1:2	I-a149	1.250
Reaction2-a								
Compound I-a149(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.250	3.90	19.50	3	MC:MeOH=20:1		I-b149	0.99	
Reaction3								
Compound I-b149(g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	0.970	0.780	0.71	50.00	5	nHx:EA=1:2	I-c149	1.500
Reaction4-b								
Compound I-c149(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.500	0.230	20.00	2	MC:MeOH=20:1		0.83	22.63	
ESI-MS(M ⁺ +1):557								
1H-NMR(CD ₃ OD):(two rotamer) δ 0.62 and 0.84(9H, s), 0.88 and 1.35(2H, s), 1.40(9H, s), 2.45 and 2.82(3H, s), 2.84-2.95(3H m), 3.04 and 3.10(3H, s), 3.23(1H, dd, J=14.7, 4.9Hz), 4.65(1H, dd, J=8.0, 2.3Hz), 5.28(1H, m), 5.45(1H, dd, J=11.8, 5.1Hz), 6.63(1H, d, J=7.9Hz), 6.88(1H, dd, J=8.0, 2.3Hz), 7.01(2H, m), 7.10(1H, d, J=2.3Hz), 7.25(2H, dd, J=8.5, 5.4Hz)								

Table D-150A

Example 150A(less polar)

Phe(4-F)-N-Me-Ala(β -CF₃)-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ CF ₃ :L,D-mixture								
Reaction1								
Compound T4(g)	Compound I13(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.560	0.560	0.51	20.00	5.000	nHx:EA=1:1	I-a150	0.980
Reaction2-b								
Compound I-a150(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.980	0.500	20.00	2	MC:MeOH =15:1		I-b150A	0.360(less polar)	
						I-b150B	0.280(more polar)	
Reaction3								
Compound I-b150A(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.360	0.310	0.270	0.27	15.00	12	nHx:EA=1:1	I-c150A	0.32
Reaction4-b								
Compound I-c150A(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.310	0.150	10.00	2	EA:MeOH =15:1		0.200	18.66	
ESI-MS(M ⁺ +1): 569								
1H-NMR(CD3OD):(two rotamers) δ 1.38 and 1.41(9H, s), 2.20, 2.56, 2.91, and 2.99(6H, s), 2.38-3.03(4H, m), 3.25 and 3.31(1H, d, J=4.8Hz), 3.72(1H, t, J=7.2Hz), 4.73(1H, brs), 5.53 and 5.57(1H, d, J=4.6Hz), 5.80(1H, q, J=4.4Hz), 6.55-6.79(2H, m), 7.00-7.15(3H, m), 7.25-7.30(2H, m)								

Phe(4-F)-N-Me-Ala(β -CF₃)-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ CF ₃ :L,D-mixture								
Reaction3								
Compound I-b150B(g)	Compound P4(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.270	0.240	0.200	0.20	15.00	12.00	nHx:EA =1:1	I-c150B	0.300
Reaction4-b								
Compound I-c150B(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.300	0.150	10.00	2	EA:MeOH =20:1	0.170	21.51		
ESI-MS(M ⁺ +1): 569								
1H-NMR(CD ₃ OD):(two rotamers) δ 1.40(9H, s), 2.19-2.40(2H, m), 2.73 and 2.76(1H, d, J=7.0Hz), 2.89(3H, s), 2.92-2.96(1H, m), 2.98(3H, s), 3.21 and 3.24(1H, d, J=6.1Hz), 4.03(1H, t, J=7.2Hz), 4.52-4.61(1H, m), 5.36(1H, q, J=5.5Hz), 5.61(1H, t, J=7.0Hz), 6.67(1H, d, J=8.0Hz), 6.89(1H, dd, J=7.9, 2.4Hz), 7.01-7.10(3H, m), 7.24-7.29(2H, m)								

Table D-151

Example 151

Phe(4-F)-N-Me-Chg-N-Me-Tyr(3-tBu)-NH₂

R								
c-Hex								
Reaction1								
Compound T4 (g)	Compound I14(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.290	1.500	2.650	1.45	30.00	20	nHx:EA=1:1	I-a151	0.700
Reaction2-a								
Compound I-a151(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.700	4.00	20.00	4	MC:MeOH =20:1		I-b151	0.400	
Reaction3								
Compound I-b151(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.400	0.380	0.760	0.41	20.00	20	nHx:EA=1:1	I-c151	0.500
Reaction4-a								
Compound I-c151(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.500	4.00	20.00	4	MC:MeOH =20:1		0.400	20.140	
ESI-MS(M ⁺ +1): 569								
1H-NMR(CDCI ₃): (two rotamers) δ 0.72-1.68(10 H, m), 1.35 and 1.40(9H, s), 1.82-2.10(1H, m), 2.30-2.65(1H, m), 2.52(3H,s), 2.70-2.90(1H, m), 2.75(3H, s), 2.75-2.90(1H, m), 3.05-3.40(3H, m), 3.60-3.85(1H, m), 5.05-5.20(2H, m), 6.35-6.75(2H, m), 6.75-7.20(5H, m)								

Table D-152

Example 152

Phe(4-F)-N-Me-D-Chg-N-Me-Tyr(3-tBu)-NH₂

R								
c-Hex:D								
Reaction1								
Compound T4 (g)	Compound I15(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.620	1.520	0.69	20.00	20	nHx:EA=1:1	I-a152	0.540
Reaction2-a								
Compound I-a152(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.540	3.00	15.00	4	MC:MeOH =20:1		I-b152	0.250	
Reaction3								
Compound I-b152(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.250	0.240	0.470	0.26	15.00	20	nHx:EA=1:1	I-c152	0.350
Reaction4-a								
Compound I-c152(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.350	3.00	10.00	4	MC:MeOH =20:1		0.27	22.040	
ESI-MS(M ⁺ +1): 569								
1H-NMR(CDCI3): (two rotamers) δ 0.65-1.70(11H, m), 1.38(9H, s), 2.15-2.35(1H, m), 2.25(3H, s), 2.75-3.05(1H, m), 2.95(3H, s), 3.10-3.25(3H, m), 5.20-5.27(2H, m), 5.55-5.65(1H, m), 6.15-6.25(2H, m), 6.54 and 6.57(2H, d, J=8.4 Hz), 6.75-6.95(1H, m), 7.05-7.15(2H, m)								

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Table D-153

Example 153

Phe(4-F)-N-Me-Cha-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ c-Hex								
Reaction1								
Compound T4 (g)	Compound I16 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.950	1.300	1.150	1.10	38.00	15	nHx:EA=1:1	I-a153	1.600
Reaction2-a								
Compound I-a153 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.600	4.80	24.00	3	MC:MeOH =20:1		I-b153	0.840	
Reaction3								
Compound I-b153 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.840	0.680	0.620	0.60	20.00	15	nHx:EA=1:1	I-c153	1.100
Reaction4-a								
Compound I-c153 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.100	2.40	12.00	3	MC:MeOH =30:1		0.50	21.154	
ESI-MS(M ⁺ +1): 583								
1H-NMR(CDCl ₃): (two rotamers) δ 0.09-1.88(13H, m), 1.35 and 1.26(9H, s), 2.32-2.80(2H, m), 2.46 and 2.74(3H, s), 2.83-3.27(3H, m), 2.99 and 3.03(3H, s), 3.59-3.73 and 3.81-3.95(1H, m), 4.62-4.74 and 5.11-5.25(1H, m), 5.27-5.59(2H, m), 6.08(1/2H, brs), 6.44 and 6.63(1H, d, J=7.9-8.3Hz), 6.77 and 6.87(1H, dd, J=7.2-7.5 1.8-1.9Hz), 6.92-7.20(5H, m), 7.59(1/2H, brs)								

T02121" 6T206360

Table D-154

Example 154

Phe(4-F)-N-Me-D-Cha-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ c-Hex:D								
Reaction1								
Compound T4 (g)	Compound I17 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.730	1.000	0.900	0.80	29.00	15	nHx:EA=1:1	I-a154	1.200
Reaction2-a								
Compound I-a154(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.200	3.60	18.00	3	MC:MeOH =20:1		I-b154	0.740	
Reaction3								
Compound I-b154(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.740	0.600	0.540	0.50	17.00	15	nHx:EA=1:1	I-c154	0.900
Reaction4-a								
Compound I-c154 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.900	2.00	10.00	3	MC:MeOH =30:1		0.24	25.144	
ESI-MS(M ⁺ +1): 583								
1H-NMR(CDCl ₃): δ 0.62-1.37(13H, m), 1.37(9H, m), 2.67-3.10(7H, m), 2.88(3H, s), 2.97(3H, s), 3.30 and 3.35(1H, d, J=3.3-3.4Hz), 3.95(1H, t, J=6.9Hz), 5.04 and 5.08(1H, d, J=4.2-4.5Hz), 5.43 and 5.47(1H, d, J=5.4-5.8Hz), 5.52(1H, brs), 6.37(1H, brs), 6.58(1H, d, J=7.9Hz), 6.79-7.09(4H, m), 7.11(1H, d, J=5.2Hz), 7.14(1H, d, J=5.4Hz)								

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Table D-155

Example 155

Phe(4-F)-N-Me-Phe-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ Ph								
Reaction1								
Compound T4 (g)	Compound I18 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	1.000	1.230	0.89	20.00	20	nHx:EA =1:1	I-a155	1.390
Reaction2-b								
Compound I-a155(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.390	0.300	20.00	20	MC:MeOH =20:1		I-b155	0.840	
Reaction3								
Compound I-b155(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.710	0.720	0.52	15.00	20	nHx:EA =1:1	I-c155	0.997
Reaction4-a								
Compound I-c155(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.997	3.00	10.00	4	MC:MeOH =20:1		0.68	19.710	
ESI-MS(M ⁺ +1): 577								
1H-NMR(CDCl ₃):(two rotamers) δ 1.40 and 1.42(9H, s), 2.54(3H, s), 2.61-3.04(5H, m), 3.15-3.39(4H, m), 3.67-3.85(1H, m), 5.32-5.72(2H, m), 6.57-6.72(1H, m), 6.98-7.29(10H, m)								

T02227 " 6T205350

Table D-156

Example 156

Phe(4-F)-N-Me-D-Phe-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ Ph:D								
Reaction1								
Compound T4 (g)	Compound I19 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.800	0.800	1.230	0.89	20.00	20	nHx:EA=1:1	I-a156	1.140
Reaction2-a								
Compound I-a156(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.140	3.00	10.00	4	MC:MeOH =20:1		I-b156	0.990	
Reaction3								
Compound I-b156(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.770	0.710	0.720	0.52	20.00	20	nHx:EA=1:1	I-c156	0.960
Reaction4-a								
Compound I-c156(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.960	3.00	10.00	4	MC:MeOH =20:1		0.73	21.960	
ESI-MS(M ⁺ +1): 577								
1H-NMR(CDCl ₃): δ 1.42(9H, s), 2.47-2.65(4H, m), 2.97-3.25(2H, m), 3.04(3H,s), 3.15(3H, s), 3.32-3.51(3H, m), 4.01-4.15(1H, m), 6.75-6.80(1H, m), 6.82-7.45(1H, m)								

T0221" 5T205860

[illegible][illegible][illegible][illegible]

Table D-158

Example 158

Phe(4-F)-N-Me-D-Phe(4-F)-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ Phe(4-F):D								
Reaction1								
Compound T4 (g)	Compound I21 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.700	1.000	0.850	0.80	27.00	18	nHx:EA=1:2	I-a158	1.120
Reaction2-a								
Compound I-a158 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.120	3.30	16.50	3	MC:MeOH =20:1		I-b158	0.880	
Reaction3								
Compound I-b158 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.880	0.560	0.500	0.50	16.00	15	nHx:EA=1:2	I-c158	0.900
Reaction4-a								
Compound I-c158 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.900	2.00	10.00	3	MC:MeOH =20:1		0.30	23.049	
ESI-MS(M ⁺ +1): 595								
1H-NMR(CDCl ₃): (two rotamers) d 1.34 and 1.37(9H, s), 2.38-2.51(1H, m), 2.53-2.82(5H, m), 2.86(3H, s), 2.88(3H, s), 3.04-3.15(1H, m), 3.21 and 3.26(1H, d, J=6.4-6.3), 3.78-3.95(1H, m), 5.26-5.38(1H, m), 5.38-5.52(1H, m), 5.62(1H, brs), 6.27(1H, brs), 6.79(1H, d, J=8.1Hz), 6.78(1H, d, J=8.7Hz), 6.83-7.22(9H, m)								

Table D-159

Example 159

Phe(4-F)-N-Me-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ Ph(4-Cl)								
Reaction1								
Compound T4 (g)	Compound I22 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.080	1.630	1.330	0.91	20.00	16	nHx:EA=1:1	I-a159	2.000
Reaction2-a								
Compound I-a159(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
2.000	5.60	25.00	1	MC:MeOH =20:1		I-b159	1.13	
Reaction3								
Compound I-b159 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.130	0.861	0.777	0.53	20.00	3	nHx:EA=1:1	I-c159	0.908
Reaction4-a								
Compound I-c159(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.908	1.96	10.00	3	MC:MeOH =20:1		0.625	21.59	
ESI-MS(M ⁺ +1):612								
1H-NMR(CDC1 ₃): (two rotamers) d 1.28 and 1.35(9H,s), 2.38 and 2.55(3H, s), 2.40-3.32(6H, m), 2.85 and 3.0(3H, s), 3.56 and 3.72(1H, t, J = 8.8Hz), 4.92(2/5H, m), 5.20-5.50(5/2H, m), 5.60 and 5.78(3/5H, brs), 6.35-7.40(25/2H, m)								

Table D-160

Example 160

Phe(4-F)-N-Me-D-Phe(4-Cl)-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ Ph(4-Cl):D								
Reaction1								
Compound T4 (g)	Compound I22 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.519	0.781	0.639	0.44	10.00	16	nHx:EA=1:1	I-a160	0.947
Reaction2-a								
Compound I-a160(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.947	5.60	15.00	1	MC:MeOH =20:1		I-b160	0.624	
Reaction3								
Compound I-b160 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.130	0.476	0.430	0.30	15.00	3	nHx:EA=1:1	I-c160	0.46
Reaction4-a								
Compound I-c160(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.460	1.00	5.00	3	MC:MeOH =20:1		0.300	19.53	
ESI-MS(M ⁺ +1):612								
1H-NMR(CDCl ₃): d 1.35(9H,s), 1.30-2.96(5H, m), 2.88(3H, s), 2.89(3H, s), 3.03-3.35(1H, m), 3.83(3/4H, m), 5.29(2H, s), 5.43(6/4H, m), 6.20(3/4H, brs), 6.52(1H, d, J=8.8Hz), 6.78(1H, d, J=8.8Hz), 6.90-7.32(10H, m)								

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Table D-161

Example 161

Phe(4-F)-N-Me-Tyr-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ Ph(4-OH)								
Reaction1								
Compound T4 (g)	Compound I24 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	2.600	1.730	1.09	30.00	3	nHx:EA=1:1	I-a161	2.610
Reaction2-a								
Compound I-a161(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
2.610	6.47	33.00	3	MC:MeOH =20:1		I-b161	1.300	
Reaction3								
Compound I-b161 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.300	1.200	0.964	0.70	30.00	3	nHx:EA=1:1	I-c161	1.880
Reaction4-b								
Compound I-c161(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.880	0.282	40.00	3	MC:MeOH =20:1		0.500	17.94	
ESI-MS(M ⁺ +1):593								
1H-NMR(CD ₃ OD): (two rotamers) d 1.41 and 1.42(9H,s), 2.32 and 2.39(3H, s), 2.90 and 3.07(3H, s), 2.59-3.50(7H, m), 3.72 and 3.85(1/2H, m), 5.05 and 5.30(1/2H, m), 5.60(1H, m), 6.50-7.43(11H, m)								

Table D-162

Example 162

Phe(4-F)-N-Me-D-Tyr-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ Ph(4-OH):D								
Reaction1								
Compound T4 (g)	Compound I25 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.920	2.000	1.220	0.77	30.00	3	nHx:EA=1:1	I-a162	1.550
Reaction2-b								
Compound I-a162(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.550	0.233	20.00	12	MC:MeOH =20:1		I-b162	0.977	
Reaction3								
Compound I-b162 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.977	1.080	0.871	0.64	20.00	3	nHx:EA=1:1	I-c162	1.330
Reaction4-b								
Compound I-c162(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
1.330	0.200	30.00	3	MC:MeOH =20:1		0.500	18.54	
ESI-MS(M ⁺ +1):593								
1H-NMR(CD ₃ OD): δ 1.45(9H,s), 2.42-2.75(4H, m), 3.02(3H, s), 2.34-3.15(2H, m), 3.32(1/5H, dd, J =7.6, 8.8Hz), 4.03(4/5H, t, J=8.8Hz), 5.42-5.65(2H, m), 6.65-7.25(12H, m)								

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Table D-163

Example 163

Phe(4-F)-N-Me-Ala(β -2-thienyl)-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ (2-Thienyl)								
Reaction1								
Compound T4 (g)	Compound I26 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.670	0.916	0.820	0.56	20.00	16	nHx:EA=1:1	I-a163	1.280
Reaction2-a								
Compound I-a163(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.280	3.80	19.00	3	MC:MeOH =20:1		I-b163	0.513	
Reaction3								
Compound I-b163 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.513	0.418	0.379	0.30	20.00	3	nHx:EA=1:1	I-c163	0.587
Reaction4-a								
Compound I-c163(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.587	1.32	10.00	3	MC:MeOH =20:1		0.35	23.7	
ESI-MS(M ⁺ +1):583								
1H-NMR(CDCl ₃ + CD ₃ OD): (two rotamers) δ 1.30 and 1.35(9H,s), 1.80(1/3H, m), 2.25, 2.58 and 2.88, 3.0(6H, s), 2.0-3.25(5H, m), 3.35(2/3H, m), 3.60(1H, m), 4.90(1/3H, m), 5.27(2/3H, m), 5.37-5.64(1H, m), 6.40-6.72(2H, m), 6.72-7.20(8H, m)								

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Table D-164

Example 164

Phe(4-F)-N-Me-D-Ala(β -2-thienyl)-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ (2-Thienyl):D								
Reaction1								
Compound T4 (g)	Compound I26 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.760	1.040	0.930	0.64	20.00	16	nHx:EA=1:1	I-a164	1.430
Reaction2-a								
Compound I-a164(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.430	4.43	25.00	3	MC:MeOH =20:1		I-b164	0.500	
Reaction3								
Compound I-b164 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.400	0.360	0.28	20.00	3	nHx:EA=1:1	I-c164	0.857
Reaction4-a								
Compound I-c164(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.857	1.92	15.00	3	MC:MeOH =20:1		0.33	21.7	
ESI-MS(M ⁺ +1):583								
1H-NMR(CDCI ₃): δ 1.35(9H,s), 2.17-3.20(7H, m), 2.91(3H, s), 2.95(3H, s), 3.28(1/2H, dd, J=15.8, 7.9Hz), 3.85(1/2H, t, J=7.9Hz), 5.35 and 5.45(2H, m), 5.65(1H, brs), 6.28(2/3H, brs), 6.48-7.30(28/3H, m)								

Table D-165

Example 165

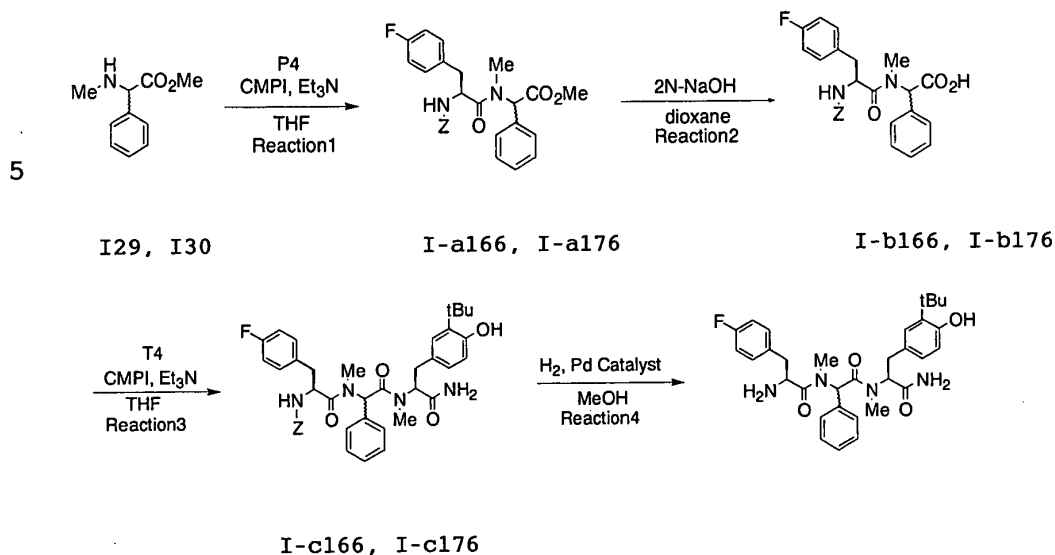
Phe(4-F)-N-Me-Ala(β -c-Pr)-N-Me-Tyr(3-tBu)-NH₂

R								
CH ₂ c-Pr								
Reaction1								
Compound T4 (g)	Compound I28 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.820	1.100	1.000	0.90	33.00	17	nHx:EA=1:1	I-a165	1.260
Reaction2-b								
Compound I-a165 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.260	0.120	24.00	3	MC:MeOH =30:1		I-b165	0.600	
Reaction3								
Compound I-b165 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	0.540	0.490	0.50	16.00	18	nHx:EA=1:1	I-c165	0.590
Reaction4-a								
Compound I-c165 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.590	1.40	7.00	3	MC:MeOH =30:1		0.300	18.61	
ESI-MS(M ⁺ +1): 541								
1H-NMR(CD ₃ OD): (two rotamers) δ 0.85-0.78(5H, m), 1.39-1.91(2H, m), 1.47 and 1.49(9H, s), 2.34 and 2.69(3H, s), 2.49-3.38(4H, m), 2.98 and 3.03(3H, s), 3.75-3.48(1H, m), 5.06-5.15 and 5.49-5.67(2H, m), 6.65-6.88(2H, m), 7.04-7.43(5H, m)								

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Scheme 10 shows the synthesis process of Examples 166 and 176.

Scheme 10: Synthesis process of Examples 166 and 176



The synthesis process in scheme 10 is explained below.

10 Reaction step 1)

To solutions of Compound P4, Compounds I29 and I30 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a166 and I-a176.

20

Reaction step 2)

To solutions of Compounds I-a166 and I-a176 in

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dioxane, 2N NaOH was added and stirred at room temperature. The reaction mixtures were adjusted to pH 3 to 4 by the addition of 1N HCl, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-b166 and I-b176.

10 Reaction step 3)

To solutions of Compounds I-b166 and I-b176, Compound T4 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-c166 and I-c176.

20

Reaction step 4)

To solutions of Compounds I-c166 and I-c176 in methanol, Pd(OH)₂ was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd(OH)₂, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

Examples conducted according to Scheme 10 are shown
in Tables D-166 and D-176.

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Table D-166

Example 166

Phe(4-F)-N-Me-Phg-N-Me-Tyr(3-tBu)-NH₂

Reaction1								
Compound I29 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.630	1.000	1.170	1.22	30.00	3	nHx:EA =1:1	I-a166	1.070

Reaction2							
Compound I-a166(g)	2N NaOH (ml)	dioxane (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
1.070	2.50	20.00	3	MC:MeOH =20:1	I-b166	1.030	

Reaction3								
Compound I-b166 (g)	Compound T4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.030	0.504	0.668	0.42	20.00	3	nHx:EA =1:1	I-c166	0.595

Reaction4						
Compound I-c166(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.595	0.100	10.00	3	MC:MeOH =20:1	0.480	20.00

ESI-MS(M⁺+1):563

1H-NMR(CD₃OD): (two rotamers) δ 1.40 and 1.49(9H,s), 2.75 and 2.90(3H, s), 2.95 and 3.15(3H, s), 2.53-3.50(5H, m) 4.12(1H, m), 4.74 and 5.32(1H, m), 6.40-7.58(15H, m)

Table D-176

Example 176

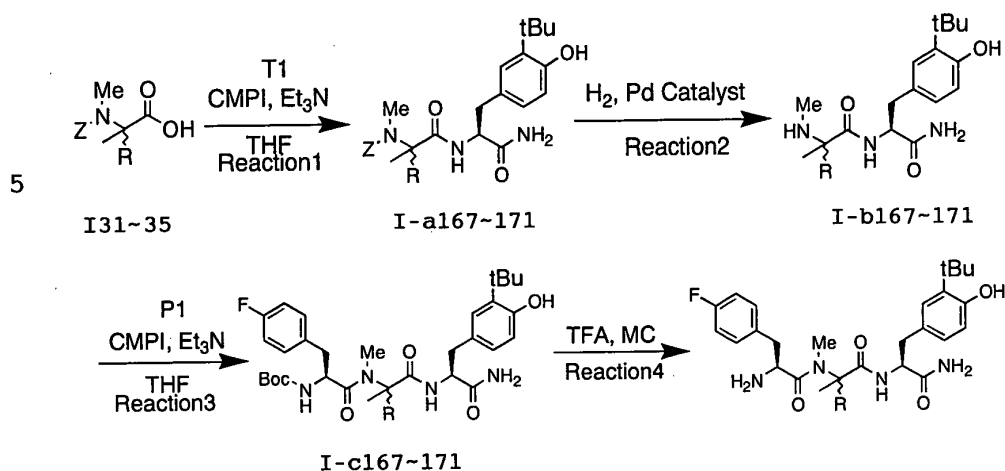
Phe(4-F)-N-Me-D-Phg-N-Me-Tyr(3-tBu)-NH₂

Reaction1								
Compound I30 (g)	Compound P4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.646	2.160	2.300	1.45	20.00	3	nHx:EA =1:1	I-a176	1.030
Reaction2								
Compound I-a176(g)	2N NaOH (ml)	dioxane (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.030	2.40	20.00	3	MC:MeOH =20:1		I-b176	0.540	
Reaction3								
Compound I-b176 (g)	Compound T4 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.540	0.268	0.355	0.22	10.00	3	nHx:EA =1:1	I-c176	0.450
Reaction4								
Compound I-c176(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.450	0.070	10.00	3	MC:MeOH =20:1		0.270	20.98	
ESI-MS(M ⁺ +1):563								
1H-NMR(CD ₃ OD): δ 1.46(9H,s), 2.50(3H, s), 2.82(3H, s), 2.72-3.13(3H, m), 3.402H, m), 4.20(1H, m), 5.48(1H, dd, J=13.2, 6.2Hz), 6.25(1H, brs), 6.35(2H, d, J=8.8Hz), 6.75(1H, d, J=8.8Hz), 6.90(1H, dd, J=8.8, 1.7Hz), 7.05-7.45(8H, m)								

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Scheme 11 shows the synthesis process of Examples 167-171.

Scheme 11: Synthesis scheme of Examples 167-171



The synthesis process in scheme 11 is explained below.

10 Reaction step 1)

To solutions of Compound T1, Compounds I31 to I35 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated
15 brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a167 to I-a171.

20

Reaction step 2)

To solutions of Compounds I-a167 to I-a171 in methanol, Pd/C was added and stirred in a hydrogen

atmosphere at room temperature. After filtering off the
Pd/C, the filtrates were concentrated under reduced
pressure; the thus obtained residues were purified by
column chromatography (silica gel) to give Compounds I-b167
5 to I-b171.

Reaction step 3)

To solutions of Compounds I-b167 to I-b171, Compound
P1 and CMPI in THF, TEA was added under cooling and stirred
10 at room temperature. The reaction mixtures were mixed with
water, extracted with ethyl acetate, washed with saturated
brine, dried over anhydrous magnesium sulfate and filtered.
The filtrates were concentrated under reduced pressure; the
thus obtained residues were purified by column
15 chromatography (silica gel) to give Compounds I-c167 to I-
c171.

Reaction step 4)

To solutions of Compounds I-c167 to I-c171 in
20 dichloromethane, TFA was added under cooling and stirred at
room temperature. The reaction mixtures were concentrated
under reduced pressure, neutralized by the addition of a
saturated NaHCO_3 aqueous solution, extracted with ethyl
acetate, dried over anhydrous magnesium sulfate and
25 filtered. The filtrates were concentrated under reduced
pressure; the thus obtained residues were purified by
column chromatography (silica gel) to give the titled
compounds.

Examples conducted according to Scheme 11 are shown
in Tables D-167 to D-171.

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Table D-167

Example 167

Phe(4-F)-N-Me- α -Me-Phe-Tyr(3-tBu)-NH₂

R								
CH ₂ Phe								
Reaction1								
Compound T1 (g)	Compound I31 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.570	1.180	0.900	0.80	24.00	5	nHx:EA =1:2	I-a167	0.360
Reaction2								
Compound I-a167 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
0.360	0.040	6.00	3		I-b167		0.260	
Reaction3								
Compound I-b167 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.260	0.420	0.780	0.40	6.30	120	nHx:EA =1:2	I-c167	0.060
Reaction4								
Compound I-c167 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.060	0.20	0.70	3	MC:MeOH =20:1		0.01	21.813	
ESI-MS(M ⁺ +1): 577								
1H-NMR(CDCl ₃): δ 1.30(3H, s), 1.34(9H, s), 2.37-2.62(3H, m), 2.51(3H, s), 3.07(1H, d, J=14.5Hz), 3.24-3.41(2H, m), 3.73(1H, t, J=8.3Hz), 4.48-4.57(1H, m), 5.37-5.58(2H, m), 6.50(1H, d, J=9.0Hz), 6.75(1H, d, J=9.3Hz), 6.77(1H, s), 6.97-7.37(9H, m)								

Table D-168

Example 168

Phe(4-F)-N-Me- α -Me-Phe-Tyr(3-tBu)-NH₂:Diastereomeric mixture

R								
CH ₂ Phe:D								
Reaction1								
Compound T1 (g)	Compound I32 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.390	0.820	0.640	0.60	16.00	5	nHx:EA =1:2	I-a168	0.670
Reaction2								
Compound I-a168 (g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
0.670	0.060	12.00	3		I-b168		0.500	
Reaction3								
Compound I-b168 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.810	1.400	1.20	12.00	120	nHx:EA =2:1	I-c168	0.210
Reaction4								
Compound I-c168 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.210	0.53	2.60	3	MC:MeOH =20:1		0.070	20.15/20.93	
ESI-MS(M ⁺ +1): 577								
1H-NMR(CDCl ₃): (two rotamers) δ 1.12-1.41(3H, m), 1.35(9H, s), 1.98 and 2.40(3H, s), 2.36(1H, s), 2.46-2.78(2H, m), 2.82-3.28(4H, m), 3.42-3.83(2H, m), 4.52-4.72(1H, m), 5.38-5.56(1H, m), 5.98-6.22(1H, m), 6.61-6.28(2H, m), 6.35-7.38(10H, m)								

Table D-169

Example 169

Phe(4-F)-N-Me- α -Me-Leu-Tyr(3-tBu)-NH₂

R								
i-Bu								
Reaction1								
Compound T1 (g)	Compound I33 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.560	1.770	2.310	1.68	60.00	12	nHx:EA:MC = 1:1.5:1	I-a169	2.390
Reaction2								
Compound I-a169(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
2.390	0.360	80.00	12		I-b169		1.490	
Reaction3								
Compound I-b169(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.490	1.230	1.510	1.10	78.00	12	nHx:EA=1:2	I-c169	0.910
Reaction4-a								
Compound I-c169(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.850	1.30	1.30	4	MC:MeOH =25:1		0.130	21.50	
ESI-MS(M ⁺ +1):543								
1H-NMR(CD ₃ OD): δ 0.79(6H, t, J=7.0Hz), 1.27(3H, s), 1.46(9H, s), 1.51-1.79(3H, m), 2.54-2.67(2H, m), 2.76(3H, s), 3.04(1H, dd, J=14.3, 5.6Hz), 3.21(1H, dd, J=14.0, 6.8Hz), 3.81(1H, t, J=6.5-7.1Hz), 4.56(1H, dd, J=14.1, 6.4Hz), 5.39(1H, brs), 5.78(1H, brs), 6.61(1H, d, J=7.8Hz), 6.93-7.14(6H, m), 7.45(1H, brs)								

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Table D-170

Example 170

Phe(4-F)-N-Me- α -Me-D-Abu-Tyr(3-tBu)-NH₂

R								
Et:D								
Reaction1								
Compound T1(g)	Compound I34(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.147	0.150	0.220	0.16	3.00	12	nHx:EA =1:1	I-a170	0.251
Reaction2								
Compound I-a170(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
0.250	0.150	5.00	3		I-b170		0.151	
Reaction3								
Compound I-b170(g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.150	0.18	0.160	0.12	3.00	16	nHx:EA =1:1	I-c170	0.145
Reaction4								
Compound I-c170(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.140	0.60	3.00	2.5	EA:MeOH =20:1		0.075	19.5	
ESI-MS(M ⁺ +1):515								
1H-NMR(CDCl ₃): δ 0.57(3H, t, J=7.6Hz), 1.21(3H, s), 1.37(9H, s), 1.63-1.82(2H, m), 1.70-1.92(2H, m), 2.59-2.71(2H, m), 2.72(3H, s), 3.03-3.21(2H, m), 3.84(1H, t, J=7.0Hz), 4.60(1H, q, J=6.0Hz), 5.51(1H, brs), 5.84(1H, d, J=7.3 Hz), 6.62(1H, d, J=8.0Hz), 6.91-7.03(5H, m), 7.09-7.14(2H, m), 7.54(1H, s)								

Table D-171

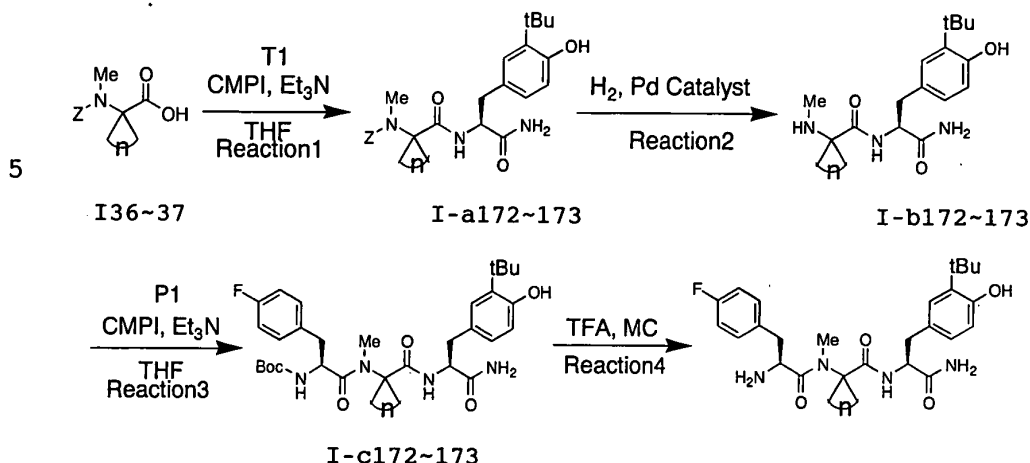
Example 171

Phe(4-F)-N-Me- α -Me-D-Val-Tyr(3-tBu)-NH₂

R								
i-Pr:D								
Reaction1								
Compound T1 (g)	Compound I35 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.144	0.170	0.150	0.17	3.6	12	nHx:EA=3:2	I-a171	0.120
Reaction2								
Compound I-a171(g)	Pd/C (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
0.120	0.020	5.00	1.5		I-b171		0.080	
Reaction3								
Compound I-b171(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.080	0.190	0.170	0.12	2.00	30	nHx:EA=2:3	I-c171	0.050
Reaction4								
Compound I-c171(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.050	0.36	1.00	3	MC:MeOH =7:1		0.02	20.40	
ESI-MS(M ⁺ +1):529								
1H-NMR(CDCl ₃): δ 0.69(3H, d, J=6.7Hz), 0.85(3H, d, J=6.7Hz), 1.16(3H, s), 1.36(9H, s), 1.76-1.92(1H, m), 2.27-2.44(1H, m), 2.52-2.70(2H, m), 2.82(3H, s), 3.03-3.24(2H, m), 4.54-4.62(1H, m), 5.47(1H, brs), 5.76(1H, d, J=7.5Hz), 6.60(1H, d, J=8.1Hz), 6.87-7.06(4H, m), 7.09-7.16(2H, m), 7.37(1H, brs)								

Scheme 12 shows the synthesis process of Examples 172 and 173.

Scheme 12: Synthesis scheme of Examples 172 and 173



The synthesis process in scheme 12 is explained below.

10 Reaction step 1)

To solutions of Compound T1, Compounds I36 and I37 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixtures were mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give Compounds I-a172 and I-173.

20

Reaction step 2)

To solutions of Compounds I-a172 and I-a173 in methanol, Pd(OH)₂ was added and stirred in a hydrogen

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atmosphere at room temperature. After filtering off the
Pd(OH)₂, the filtrates were concentrated under reduced
pressure; the thus obtained residues were purified by
column chromatography (silica gel) to give Compounds I-b172
5 and I-b173.

Reaction step 3)

To solutions of Compounds I-b172 and I-b173, Compound
P1 and CMPI in THF, TEA was added under cooling and stirred
10 at room temperature. The reaction mixtures were mixed with
water, extracted with ethyl acetate, washed with saturated
brine, dried over anhydrous magnesium sulfate and filtered.
The filtrates were concentrated under reduced pressure; the
thus obtained residues were purified by column
15 chromatography (silica gel) to give Compounds I-c172 and
I-c173.

(Reaction step 4)

To solutions of Compounds I-c172 and I-c173 in
20 dichloromethane, TFA was added under cooling and stirred at
room temperature. The reaction mixtures were concentrated
under reduced pressure, neutralized by the addition of a
saturated aqueous NaHCO₃ solution, extracted with ethyl
acetate, dried over anhydrous magnesium sulfate and
25 filtered. The filtrates were concentrated under reduced
pressure; the thus obtained residues were purified by
column chromatography (silica gel) to give the titled
compounds.

Examples conducted according to Scheme 12 are shown
in Tables D-172 and D-173.

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Table D-172

Example 172

(2S)-N-[(N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl)carbamoyl)cyclopentyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide

5

Reaction1								
Compound T1 (g)	Compound 136 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.600	1.050	0.973	0.70	20.00	3	nHx:EA =1:1	1-a172	1.210
Reaction2								
Compound 1-a172(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)		Product		Column sol.	
1.210	0.182	30.00	3		1-b172		MC:MeOH =20:1	
Reaction3								
Compound 1-b172 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.744	1.170	1.050	0.72	20.00	52	nHx:EA =1:1	1-c172	0.518
Reaction4								
Compound 1-c172(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.518	1.330	10.00	3	MC:MeOH =20:1		0.130	19.59	
ESI-MS(M ⁺ +1):527								
1H-NMR(CDCl ₃): (two rotamers) δ 1.30 and 1.40(9H,s), 1.15-2.42(8H, m), 2.52-2.80(2H, m), 2.86 and 2.92(3H, s), 3.02-3.35(2H, m), 3.58 and 3.85(1H, m),4.30 and 4.61(1H, m), 5.68(1H, brs),6.08-6.42(1H, m), 6.51-7.39(7H, m)								

Table D-173

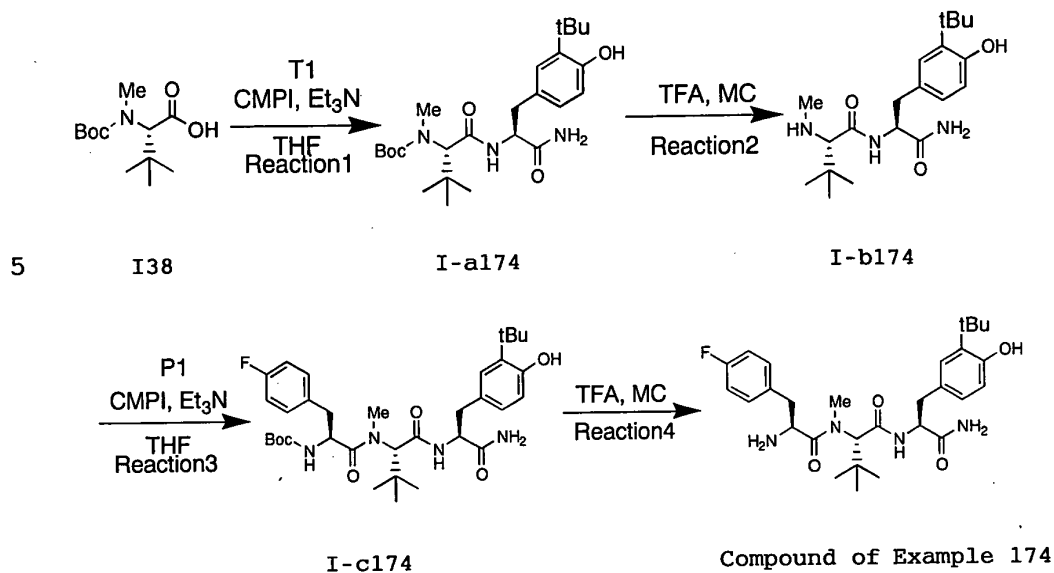
Example 173

(2S)-N-[(N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoylethyl)carbamoyl)cyclohexyl]-2-amino-3-(4-fluorophenyl)-N-methylpropanamide

Reaction1								
Compound T1(g)	Compound I37 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.708	1.310	0.766	0.84	20.00	3	nHx:EA =1:1	I-a173	1.400
Reaction2								
Compound I-a173(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)		Product		Amount (g)	
1.400	0.210	30.00	3		I-b173		0.934	
Reaction3								
Compound I-b173 (g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.930	1.410	1.270	0.87	30.00	120	nHx:EA =1:1	I-c173	0.271
Reaction4								
Compound I-c173(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.271	0.700	5.00	3	MC:MeOH =20:1		0.030	24.76	
ESI-MS(M ⁺ +1):541								
1H-NMR(CDCl ₃): (two rotamers) δ 1.30 and 1.40(9H,s), 1.15-2.50(10H, m), 2.52-2.80(2H, m), 2.86 and 2.92(3H, s), 3.02-3.35(2H, m), 3.58 and 3.85(1H, m), 4.30 and 4.61(1H, m),5.68(1H, brs),6.08-6.42(1H, m), 6.51-7.39(7H, m)								

Scheme 13 shows the synthesis process of Example 174.

Scheme 13: Synthesis scheme of Example 174



The synthesis process in scheme 13 is explained below.

Reaction step 1)

To a solution of Compound T1, Compound I38 and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a174.

Reaction step 2)

To a solution of Compound I-a174 in dichloromethane, TFA was added under cooling and stirred at room temperature.

The reaction mixture was concentrated under reduced pressure, neutralized by adding a saturated aqueous NaHCO_3 solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-b174.

(Reaction step 3)

10 To a solution of Compound I-b174, Compound P1 and
CMPI in THF, TEA was added under cooling and stirred at
room temperature. The reaction mixture was mixed with
water, extracted with ethyl acetate, washed with saturated
brine, dried over anhydrous magnesium sulfate and filtered.
15 The filtrate was concentrated under reduced pressure; the
thus obtained residue was purified by column chromatography
(silica gel) to give Compound I-c174.

(Reaction step 4)

To a solution of Compound I-cl74 in dichloromethane, TFA was added under cooling and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, neutralized by adding a saturated aqueous NaHCO_3 solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

Example conducted according to Scheme 13 is shown in Table D-174.

Table D-174

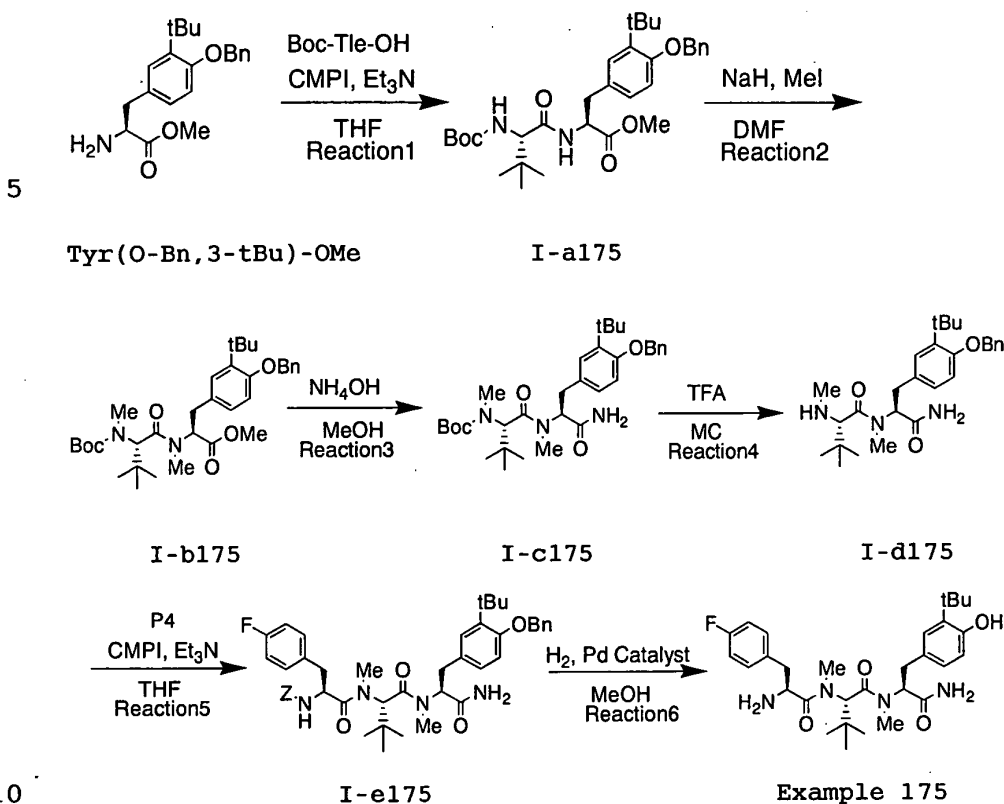
Example 174

Phe(4-F)-N-Me-Tle-Tyr(3-tBu)-NH₂

Reaction1								
Compound T1 (g)	Compound I38 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.633	0.660	0.756	0.37	15.00	24	nHx:EA =1:2	I-a174	0.670
Reaction2								
Compound I-a174(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.670	2.00	10.00	1	MC:MeOH =10:1		I-b174	0.518	
Reaction3								
Compound I-b174(g)	Compound P1 (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.518	0.809	0.730	0.40	10.00	36	nHx:EA =1:2	I-c174	0.393
Reaction4								
Compound I-c174(g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.393	1.00	5.00	1	MC:MeOH =15:1		0.162	17.54	
ESI-MS(M ⁺ +1):529								
1H-NMR(CDCl ₃):(two rotamers) δ 1.02 and 1.03 (9H,s), 1.35 and 1.36(9H, s), 2.75(3H, s), 2.70 and 3.00(4H, m), 3.12(1H, dd, J=10.3, 6.3Hz), 3.60 and 3.82(1H, m), 4.64(1H, m), 5.50(1H, brs), 5.80 and 6.00(1H, brs), 6.70(1H, s), 6.80-7.15(6H, m)								

Scheme 14 shows the synthesis process of Example 175.

Scheme 14: Synthesis scheme of Example 175



The synthesis process in scheme 14 is explained below.

Reaction step 1)

15 To a solution of Tyr(O-Bn, 3-tBu)-OMe, Compound Boc-Tle-OH and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and

20 filtered. The filtrate was concentrated under reduced

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pressure, neutralized by the addition of a saturated aqueous NaHCO_3 solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus
5 obtained residue was purified by column chromatography (silica gel) to give Compound I-d175.

Reaction step 5)

To a solution of Compound I-d175, Compound P4 and
10 CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the
15 thus obtained residue was purified by column chromatography (silica gel) to give Compound I-e175.

Reaction step 6)

To a solution of Compound I-e175 in methanol, $\text{Pd}(\text{OH})_2$
20 was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the $\text{Pd}(\text{OH})_2$, the filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give the titled compound.

25 Example conducted according to Scheme 14 is shown in Table D-175.

Table D-175

Example 175

Phe(4-F)-N-Me-Tle-N-Me-Tyr(3-tBu)-NH₂

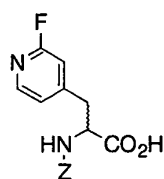
Reaction1								
Tyr(O-Bn,3-tBu)-OMe (g)	Boc-Tle-OH (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.720	1.280	1.410	1.40	34.00	12	nHx:EA=5:1	I-a175	2.200
Reaction2								
Compound I-a175 (g)	NaH (g)	Methyl Iodide(ml)	DMF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)	
2.200	0.480	2.22	22.00	1	nHx:EA=5:1	I-b175	1.930	
Reaction3								
Compound I-b175 (g)	NH ₄ OH (ml)	MeOH (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
1.930	130.00	230.00	20	nHx:EA=2:1		I-c175	0.564	
Reaction4								
Compound I-c175 (g)	TFA (ml)	MC (ml)	Reaction time (hr)	Column sol.		Product	Amount (g)	
0.680	2.78	8.00	1.5	MC:MeOH =20:1		I-d175	0.500	
Reaction5								
Compound I-d175 (g)	Compound P1(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.500	0.951	0.546	0.50	12.50	12	nHx:EA=2:1	I-d175	0.254
Reaction6								
Compound I-d175 (g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min	
0.250	0.050	10.00	3	MC:MeOH =15:1		0.098	19.280	
ESI-MS(M ⁺ +1):543								
1H-NMR(CDCl ₃): δ 0.80(9H, s), 1.37(9H, s), 2.68(1H, dd, J=13.6, 7.3Hz), 2.85-3.01(2H, m), 2.92(3H, s), 2.98(3H, s), 3.11-3.22(1H, m), 3.94(1H, t, J=7.0Hz), 5.19(1H, s), 5.22(1H, brs), 5.37(1H, dd, J=10.5, 5.6Hz), 5.98(1H, brs), 6.55(1H, d, J=7.9Hz), 6.88(1H, dd, J=8.0, 2.2Hz), 6.94-7.00(2H, m), 7.07-7.14(3H, m)								

Methods of producing Intermediates in the scheme 15 are shown as Reference Examples in the following. The structural formulae of Intermediates of Examples 177-180 are shown in Table C-5.

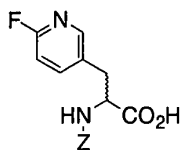
5

Table C-5

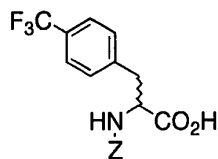
Intermediates of Examples 177-180



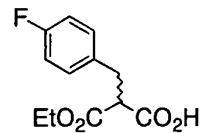
P6



P7



P8



P9

10

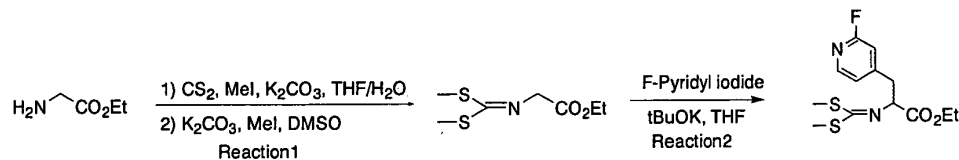
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Reference Example 27

Synthesis of Intermediates P6-P8

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediates P6-P8

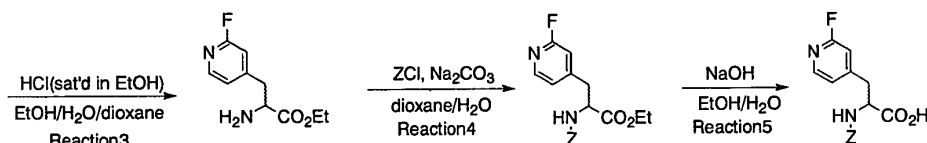


Glycine ethyl ester

I-a177-I

I-b177-I

hydrochloride



10

I-c177-I

I-d177-I

P6

The synthesis methods of Intermediates P6-P8 are explained below.

F-Pyridyl iodide [2-fluoro-4-(iodomethyl)pyridine and 2-fluoro-5-(iodomethyl)pyridine] were synthesized referring to J. Med. Chem., 1998, 41(23), 4615. P7 and P8 were synthesized according to a similar method of synthesizing P6 using the above 2-fluoro-5-(iodomethyl)pyridine and 4-(iodomethyl)-1-(trifluoromethyl)benzene.

20

Reaction step 1)

To a solution of glycine ethyl ester hydrochloride, CS₂ and water in THF, K₂CO₃ and CH₃I were added dropwise and

then stirred at room temperature. After the completion of the reaction, the reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The
 5 filtrate was concentrated under reduced pressure; to a solution of the thus obtained residue in a mixture of DMSO and water, K_2CO_3 was added dropwise gradually and then under cooling with ice, CH_3I was added dropwise gradually, followed by stirring at room temperature. The reaction
 10 mixture was mixed with water, extracted with Et_2O , washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-
 15 a177-I.

Reaction step 2)

To a solution of Compound I-a177-I and $t-BuOK$ in THF, F-pyridyl iodide was added dropwise gradually at $-78^\circ C$
 20 while stirring. The reaction mixture was mixed with water, extracted with Et_2O , washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography
 25 (silica gel) to give Compound I-b177-I.

Reaction step 3)

To a solution of Compound I-b177-I in a mixture of

chromatography (silica gel) to give Intermediate P6.

The results are shown in Tables E-46 to E-48.

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Table E-46

Intermediate P6

3-(2-fluoro-4-pyridyl)-2-

[(phenylmethoxy)carbonylamino]propanoic acid

Reaction1-a							
Gly-OEt HCl(g)	K ₂ CO ₃ (g)	Methyl iodide(ml)	CS ₂ (ml)	THF/H ₂ O (ml)	Reaction time (hr)	Product	Amount (g)
20.000	19.890	8.96	8.66	60.00 /14.00	1	Crude intermediate	27.061
Reaction1-b							
Crude intermediate (g)	K ₂ CO ₃ (g)	Methyl iodide(ml)	DMSO / H ₂ O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
12.000	8.590	3.90	60.00 / 14.00	0.5	nHx:EA =5:1	l-a177-l	11.7000
Reaction2							
l-a177-l (g)	2-fluoro-4- (iodomethyl) pyridine(ml)	tBuOK (g)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.000	2.520	1.190	32.00	2.50	nHx:EA =7:1	l-b177-l	2.480
Reaction3							
l-b177-l (g)	HCl(sat'd in EtOH) (ml)		EtOH/H ₂ O (ml)	Dioxane (ml)	Reaction time (hr)	Product	Amount (g)
2.480	11.50		11.50 / 11.50	6	16	l-c177-l	1.33
Reaction4							
l-c177-l (g)	ZCl (ml)	Na ₂ CO ₃ (g)	Dioxane/ H ₂ O (ml)		Reaction time (hr)	Product	Amount (g)
1.330	0.99	1.000	18.00 / 18.00		2	l-d177-l	1.36
Reaction5							
l-d177-l (g)	NaOH (g)	EtOH/H ₂ O (ml)		Reaction time (hr)		Amount (g)	
1.330	0.314	30.00 / 10.00		1.500		1.200	

3-(2-fluoro-5-pyridyl)-2-

Reaction1-a							
Gly-OEt HCl(g)	K ₂ CO ₃ (g)	Methyl iodide(ml)	CS ₂ (ml)	THF/H ₂ O (ml)	Reaction time (hr)	Product	Amount (g)
20.000	19.890	8.96	8.66	60.00 / 14.00	1	Crude intermediate	27.061
Reaction1-b							
Crude intermediate(g)	K ₂ CO ₃ (g)	Methyl iodide(ml)	DMSO/ H ₂ O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
12.000	8.590	3.90	60.00 / 14.00	0.5	nHex:EA	1-a178-1	11.7000
Reaction2							
1-a178-1 (g)	2-fluoro-5-(iodomethyl) pyridine(ml)	tBuOK (g)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
3.990	8.37	2.380	60.00	3.00	nHex:EA	1-b178-1	4.300
Reaction3							
1-b178-1 (g)	HCl(sat'd in EtOH)(ml)	EtOH/H ₂ O (ml)	Dioxane (ml)	Reaction time (hr)	Product	Amount (g)	
4.300	20.00	12.00 / 12.00	10.00	16	1-c178-1	1.880	
Reaction4							
1-c178-1 (g)	ZCl (ml)	Na ₂ CO ₃ (g)	Dioxane/ H ₂ O (ml)	Reaction time (hr)	Product	Amount (g)	
1.880	1.40	1.410	25.00 / 25.00	2	1-d178-1	2.940	
Reaction5							
1-d178-1 (g)	NaOH (g)	EtOH/H ₂ O (ml)	Reaction time (hr)	Product	Amount (g)		
2.620	0.606	40.00 / 10.00	1.500		2.400		

2-[(Phenylmethoxy)carbonylamino]-3-[4-(trifluoromethyl)phenyl]propanoic acid

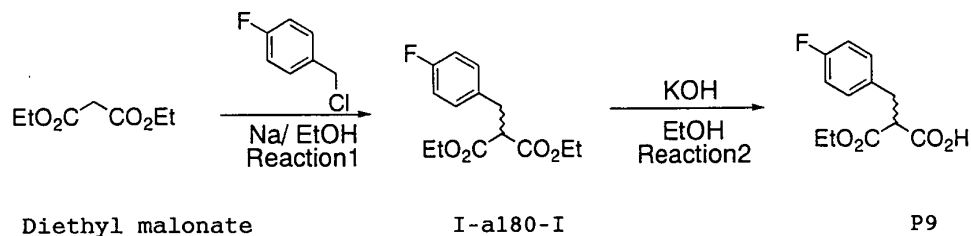
Reaction1-a							
Gly-OEt-HCl(g)	K ₂ CO ₃ (g)	Methyl iodide(ml)	CS ₂ (ml)	THF/H ₂ O (ml)	Reaction time (hr)	Product	Amount (g)
20.000	19.890	8.96	8.66	60.00 /14.00	1	Crude intermediate	27.061
Reaction1-b							
Crude intermediate(g)	K ₂ CO ₃ (g)	Methyl iodide(ml)	DMSO/ H ₂ O (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
12.000	8.590	3.90	60.00 / 14.00	0.5	nHx:EA =5:1	1-a179-I	11.700
Reaction2							
1-a179-I (g)	4-(iodomethyl)-1- (trifluoro methyl)benzene (ml)	tBuOK (g)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
2.120	3.220	1.270	40.00	2	nHx:EA =7:1	1-b179-I	3.730
Reaction3							
1-b179-I (g)	HCl (sat'd in EtOH)(ml)		EtOH/H ₂ O (ml)	Dioxane (ml)	Reaction time (hr)	Product	Amount (g)
1.620	6.50		6.50 / 6.50	3.00	16	1-c179-I	0.737
Reaction4							
1-c179-I (g)	ZCl (ml)	Na ₂ CO ₃ (g)	Dioxane/ H ₂ O (ml)	Reaction time (hr)	Product	Amount (g)	
0.737	0.45	0.450	9.00 / 9.00	1	1-d179-I	1.090	
Reaction5							
1-d177-I (g)	NaOH (g)	EtOH/H ₂ O (ml)		Reaction time (hr)		Amount (g)	
1.090	0.186	9.00 / 9.00		1.5		1.010	

(Reference Example 28)

Synthesis of Intermediate P9

The synthesis scheme is shown below.

5 Synthesis scheme of Intermediate P9



The synthesis method of Intermediates P9 is explained below.

10

Reaction step 1)

To a solution of Na-metal in ethanol, diethyl malonate and 4-(chloromethyl)-1-fluorobenzene were added dropwise and then stirred at room temperature. The reaction mixture was concentrated under reduced pressure, mixed with water, extracted with Et₂O, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give Compound I-a180-I in a crude form.

20

Reaction step 2)

To a solution of Compound I-a180-I in ethanol, KOH was added and stirred at room temperature. The reaction mixture was concentrated under reduced pressure, mixed with water and washed with Et₂O. The aqueous layer was

25

adjusted to a pH of 3-4 by the addition of 1N HCl,
extracted with ethyl acetate, washed with saturated brine,
dried over anhydrous magnesium sulfate and filtered. The
filtrate was concentrated under reduced pressure; the thus
5 obtained residue was purified by column chromatography
(silica gel) to give Intermediate P9.

Result is shown in Table E-49.

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Table E-49

Intermediate P9

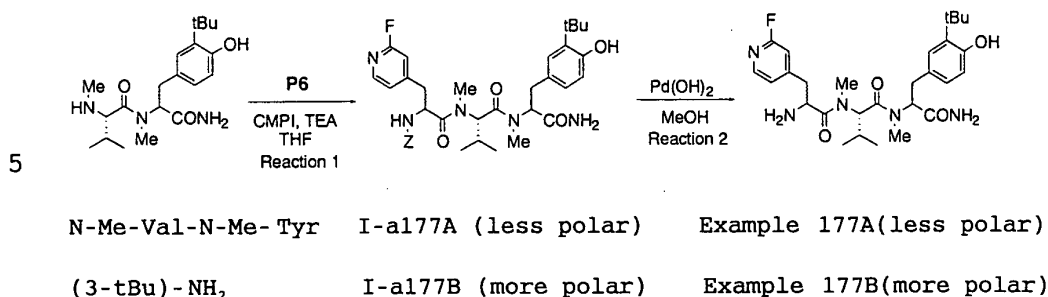
2-(Ethoxycarbonyl)-3-(4-fluorophenyl)propanoic acid

Reaction1					
Diethyl malonate (g)	4-(chloromethyl)-1- fluorobenzene (ml)	Na-metal (g)	EtOH (ml)	Product	Amount (g)
15.000	10.90	2.180	120.00	I-a180-I	25.000
Reaction2					
I-a180-I (g)	KOH (g)	EtOH (ml)	Amount (g)		
2.160	5.170	160.00	1.400		

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The synthesis scheme of Examples 177A to 179B is shown in Scheme 15.

Scheme 15: Synthesis scheme of Examples 177A to 179B



Referring to Examples 177A and 177B, the synthesis process of Scheme 15 is explained below:

Reaction step 1)

To a solution of Compound P6, N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a177A (less polar) and Compound I-a177B (more polar).

Reaction step 2)

To solutions of Compound I-a177A (less polar) and Compound I-a177B (more polar) in methanol, Pd(OH)₂ was added and stirred in a hydrogen atmosphere at room

temperature. After filtering off the $\text{Pd}(\text{OH})_2$, the filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds.

5

Example 178 (178A and 178B) and Example 179 (179A and 179B) were conducted similar to the above, except that P7 and P8 were employed, respectively, instead of P6.

10 Examples conducted according to Scheme 15 are shown in Tables D-177A to D-179B.

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Table D-177A

Example 177A:Less polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl
ethyl)-2-[2-amino-3-(2-fluoro-4-pyridyl)-N-methylpropanoyle
5 amino]-3-methyl-N-methylbutanamide

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂ (g)	Compound P6(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.776	0.886	0.711	0.45	30.00	16	nHx:EA=1:1	I-a177A	0.275
							I-a177B	0.288
Reaction2								
Compound I-a177A(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.275	0.042	20.00	3	MC:MeOH =20:1	0.160	17.50		
ESI-MS(M ⁺ +1):530								
1H-NMR(CDCl ₃): (two rotamers) δ 0.32, 0.42 and 0.60, 0.88(6H, d, J=7.1-7.9Hz), 1.37 and 1.42(9H, s), 2.00-2.20(1H, m), 2.52 and 2.91, 2.95(6H, s), 2.60-3.28(4H, m), 2.95(3H, s), 3.75(1/2H, dd, J=8.8, 6.1Hz), 3.95(1/2H, t, J=8.8Hz), 4.65 and 5.00(1H, d, J=8.8Hz), 4.96 and 5.47(1H, dd, J=8.8, 7.0Hz), 5.60 and 6.05(1H, brs), 6.60 and 6.15(1H, d, J=8.8Hz), 6.70 and 7.04(2H, m), 6.92 and 7.12(2H, m), 8.12(1H, m)								

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Table D-177B

Example 177B: more polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl
lethyl)-2-[2-amino-3-(2-fluoro-4-pyridyl)-N-methylpropanoyl
5 amino]-3-methyl-N-methylbutanamide

Reaction2						
Compound l-a177B(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.288	0.043	20.00	3	MC:MeOH =20:1	0.160	15.48
ESI-MS(M ⁺ +1):530						
¹ H-NMR(CDCl ₃): (two rotamers) δ 0.46, 0.72 and 0.78, 0.91(6H, d, J=7.1-7.9Hz), 1.32 and 1.38(9H, s), 2.15-2.40(1H, m), 2.50, 2.83, and 3.0, 3.08(6H, s), 2.40-3.40(5H, m), 3.70 and 3.90(1H, dd, J=8.8, 3.5-4.4Hz), 4.81 and 5.05(1H, d, J=9.7Hz), 4.99 and 5.52(2H, m), 6.05 and 6.49(1H, brs), 6.48 and 6.64(1H, d, J=7.9Hz), 6.74 and 6.76, 6.82(2H, brs), 6.90-7.18(2H, m), 8.12(1H, d, J=6.2Hz)						

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Table D-178A

Example 178A:less polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl
 lethyl)-2-[2-amino-3-(2-fluoro-5-pyridyl)-N-methylpropanoyl
 5 amino]-3-methyl-N-methylbutanamide

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂ (g)	Compound P7(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.000	1.140	0.917	0.58	20.00	3	nHex:EA=1:1	I-a178A	0.380
							I-a178B	0.100
Reaction2								
Compound I-a178A(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.380	0.057	10.00	3	MC:MeOH =20:1	0.210	17.76		
ESI-MS(M ⁺ +1):530								
1H-NMR(CDCl ₃): (two rotamers) δ 0.32, 0.42 and 0.60, 0.89(6H, d, J=7.1-7.9Hz), 1.37 and 1.42(9H, s), 2.00-2.30(1H, m), 2.50, 2.90 and 2.94, 2.95(6H, s), 2.58-3.29(4H, m), 3.70(1/2H, dd, J=8.8, 6.1Hz), 3.90(1/2H, t, J=8.8Hz), 4.67 and 5.04(1H, d, J=8.8Hz), 4.95 and 5.47(1H, dd, J=8.8, 7.0Hz), 5.70(1H, brs), 6.05 and 6.55(1H, brs), 6.58 and 6.65(1H, d, J=8.8Hz), 6.75-6.99(2H, m), 7.10 and 7.18(1H, brs), 7.58-7.75(1H, m), 8.12(1H, m)								

Table D-178B

Example 178B: more polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl
 lethyl)-2-[2-amino-3-(2-fluoro-5-pyridyl)-N-methylpropanoyl
 5 amino]-3-methyl-N-methylbutanamide

Reaction2						
Compound l-a178B(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.100	0.015	5.00	3	MC:MeOH =20:1	0.040	15.65
ESI-MS(M ⁺ +1):530						
¹ H-NMR(CDCl ₃): (two rotamers) δ 0.50, 0.75 and 0.77, 0.95(6H, d, J=7.1-7.9Hz), 1.32 and 1.39(9H, s), 2.00-2.30(1H, m), 2.47, 2.83 and 3.0, 3.05(6H, s), 2.18-3.42(4H, m), 3.61 and 3.82(1H, dd, J=8.8, 3.5-4.0Hz), 4.85 and 5.07(1H, d, J=9.7Hz), 5.57 and 5.70, 5.79, 6.11(2H, m and brs), 6.55 and 6.65(1H, d, J=7.9-8.8Hz), 6.73, 6.88 and 6.97(2H, m), 7.13(1H, brs), 7.60-7.75(1H, m), 7.97 and 8.05(1H, brs)						

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 Total 6226860

Table D-179A

Example 179A:less polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl
 lethyl)-2-{2-amino-N-methyl-3-[4-(trifluoromethyl)phenyl]pr
 5 opanoylamino}-3-methyl-N-methylbutanamide

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂ (g)	Compound P8(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.513	0.626	0.435	0.3	30.00	3	nHx:EA=1:1	I-a179A	0.330
							I-a179B	0.332
Reaction2								
Compound I-a179A(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.330	0.049	10.00	3	MC:MeOH=20:1	0.136	19.89		
ESI-MS(M ⁺ +1):579								
1H-NMR(CDC ₃): (two rotamers) δ 0.49, 0.74 and 0.79, 0.93(6H, d, J=6.3-6.8Hz), 1.34 and 1.39(9H, s), 2.25-2.48(1H, m), 2.53, 2.79 and 3.01, 3.05(6H, s), 2.58-3.40(4H, m), 3.74 and 3.90(1H, m), 4.87 and 5.07(1H, d, J=10.5-10.9Hz), 5.38-5.10(2H, m), 6.20(2/3H, brs), 6.40 and 6.65(1H, d, J=7.9Hz), 6.58(1/3H, brs), 6.73 and 6.97(1H, d, J=7.9-8.4Hz), 7.12(1H, m), 7.27-7.30(2H, m), 7.55-7.60(2H, m)								

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Table D-179B

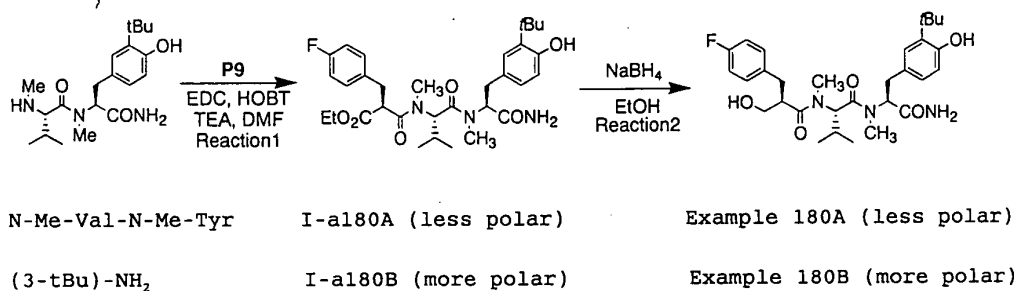
Example 179B: more polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl-ethyl)-2-{2-amino-N-methyl-3-[4-(trifluoromethyl)phenyl]propanoylamino}-3-methyl-N-methylbutanamide

Reaction2						
Compound I-a179B(g)	Pd(OH) ₂ (g)	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.332	0.049	10.00	3	MC:MeOH =20:1	0.123	22.09
ESI-MS(M ⁺ +1):579						
¹ H-NMR(CDCl ₃): (two rotamers) δ 0.33, 0.36 and 0.55, 0.87(6H, d, J=6.4-6.9Hz), 1.37 and 1.41(9H, s), 2.00-2.20(1H, m), 2.56, 2.92 and 2.98(6H, s), 2.60-3.21(4H, m), 3.77 and 3.96(1H, m), 4.67 and 5.02(1H, d, J=10.6-10.9Hz), 4.96 and 5.45(1H, dd, J=9.0-11.3, 3.4-6.0Hz), 5.67 and 6.04(1H, brs), 6.57 and 6.63(1H, d, J=7.9Hz), 6.74 and 6.94(1H, dd, J=8.0-9.8, 1.8-2.1Hz), 7.08 and 7.16(1H, d, J=1.9Hz), 7.27-7.37(2H, m), 7.52-7.60(2H, m)						

Scheme 16 shows synthesis process of Examples 180A and B.

10 Scheme 16: synthesis process of Examples 180A and B



The synthesis process of Scheme 16 is explained

15 below.

Reaction step 1)

To a solution of Compound P9, N-Me-Val-N-Me-Tyr(3-tBu)-NH₂, EDCL and HOBT in DMF, TEA was added under

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cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with Et₂O, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under
5 reduced pressure and purified by column chromatography (silica gel) to give Compound I-a180A (less polar) and Compound I-a180B (more polar).

Reaction step 2)

10 To the solutions of Compound I-a180A (less polar) and Compound I-a180B (more polar) in ethanol, NaBH₄ was added under cooling and stirred at room temperature. The reaction mixtures were mixed with a 1N HCl solution, extracted with Et₂O, washed with saturated brine, dried
15 over anhydrous magnesium sulfate and filtered. The filtrates were concentrated under reduced pressure; the thus obtained residues were purified by column chromatography (silica gel) to give the titled compounds (less polar compound and more polar compound).

20 Tables D-180A and B show Examples conducted according to Scheme 16.

Table D-180A

Example 180A: Less polar

(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl
 lethyl)-2-{2-[(4-fluorophenyl)methyl]-3-hydroxy-N-methylpro

5 panoylamino}-3-methyl-N-methylbutanamide

Reaction1									
N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂ (g)	Compound P9(g)	EDCI (g)	HOBt (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
1.500	1.29	1.030	0.824	1.08	30.00	2.5	nHc:EA=1:1	I-a180A	0.700
								I-a180B	0.820
Reaction2									
Compound I-a180A(g)	NaBH ₄ (g)	EtOH (ml)	Reaction time (hr)	Column sol.		Amount (g)	HPLC min		
0.700	0.490	30.00	3	MC:MeOH=20:1		0.17	21.83		
ESI-MS(M ⁺ +1):544									
1H-NMR(CDCl ₃): (two rotamers) δ 0.48, 0.74 and 0.76, 0.92(6H, d, J=6.0-7.2Hz), 1.35 and 1.39(9H, s), 2.05-2.50(1H, m), 2.50, 2.80 and 2.98, 3.01(6H, s), 2.40-3.36(5H, m), 3.50-3.70(2H, m), 3.50-3.70(2H, m), 4.90 and 5.08(1H, d, J=10.6Hz), 5.45(1H, m), 5.50 and 6.05(1H, brs), 5.70 and 6.20(1H, brs), 6.44 and 6.64(1H, d, J=8.8-8.3Hz), 6.73-7.15(7H, m)									

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Table D-180B

Example 180B: more polar

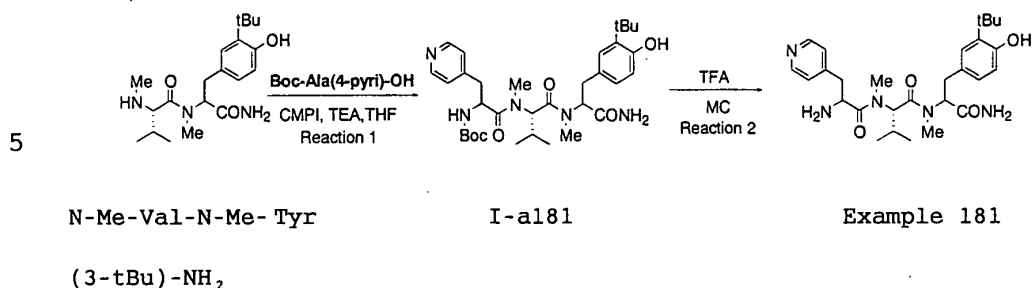
(2S)-N-((1S)-2-[3-(tert-butyl)-4-hydroxyphenyl]-1-carbamoyl
lethyl)-2-{2-[(4-fluorophenyl)methyl]-3-hydroxy-N-methylpro
5 panoylamino}-3-methyl-N-methylbutanamide

Reaction2						
Compound I-a180B(g)	NaBH ₄ (g)	EtOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.820	0.492	30.00	3	MC:MeOH =20:1	0.060	23.95
ESI-MS(M ⁺ +1):544						
¹ H-NMR(CDCl ₃): (two rotamers) δ 0.17-0.20 and 0.44, 0.84(6H, m and d, J=6.5-6.7Hz), 1.36 and 1.40(9H, s), 2.00-2.20(1H, m), 2.41 and 2.90, 2.92(6H, s), 2.67-4.00(13H, m), 4.73 and 5.00(1H, d, J=10.5Hz), 5.20 and 5.35(1H, m), 5.83 and 6.18(1H, brs), 6.38 and 6.51(1H, brs), 6.62 and 6.65(1H, d, J=7.9Hz), 6.75-7.20(8H, m)						

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The synthesis scheme of Examples 181 and 182 is shown in Scheme 17.

Scheme 17: Synthesis scheme of Examples 181 and 182



Referring to Example 181, the synthesis process of Scheme 17 is explained below:

Reaction step 1)

To a solution of Compound Boc-Ala(β-4-pyridyl)-OH, N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a181.

Reaction step 2)

To a solution of Compound I-a181 in dichloromethane, TEA was added under cooling and stirred at room temperature. The reaction mixture was concentrated under

reduced pressure, extracted with dichloromethane, washed
with saturated brine, dried over anhydrous magnesium
sulfate and filtered. The filtrate was concentrated under
reduced pressure; the thus obtained residue was purified
5 by column chromatography (silica gel) to give the titled
compound.

Compound of Example 182 was obtained according to a
similar process to Example 181 using Boc-Ala(β -4-pyridyl)-
10 OH.

Examples conducted according to Scheme 17 are shown
in Tables D-181 and D-182.

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$$\text{Ala}(\beta\text{-4-pyridyl})\text{-N-Me-Val-N-Me-Tyr(3-tBu)-NH}_2$$

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂ (g)	Boc-Ala(beta-4-pyridyl)-OH (g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.680	0.500	0.960	0.52	15.00	24	MC:MeOH =30:1	I-a181	0.800

Reaction2						
Compound I-a181(g)	TFA	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min
0.800	4.00	20.00	3	MC:MeOH =20:1	0.450	13.30

ESI-MS(M⁺+1):512

¹H-NMR(CDCl₃): (two rotamers) δ 0.40, 0.72 and 0.82, 0.96(6H, d, J=6.3-6.7Hz), 1.37 and 1.42(9H, s), 2.05-2.30(1H, m), 2.51, 2.89 and 2.94, 2.96(6H, s), 2.59-3.30(4H, m), 4.65-5.05(1H, m), 5.30(1H, s), 5.45-5.05(1H, m), 6.30-6.45(1H, m), 6.60-7.05(2H, m), 7.10-7.20(2H, m), 8.20-8.25(2H, m)

Table D-182

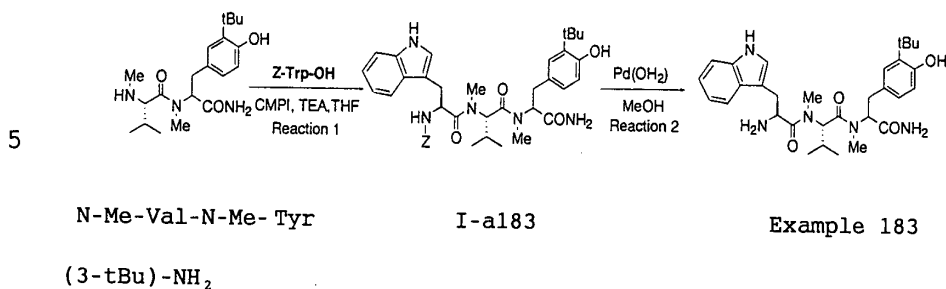
Example 182

Phe(4-CN)-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂ (g)	Boc-Phe(4-CN)-OH(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.620	0.500	0.660	0.48	15.00	24	MCMeOH =30:1	I-a182	0.900
Reaction2								
Compound I-a182(g)	TFA	MC (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.900	4.00	20.00	4	MCMeOH =20:1	0.520	16.82		
ESI-MS(M ⁺ +1):536								
1H-NMR(CDCl ₃): (two rotamers) δ 0.48, 0.76 and 0.85, 0.94(6H, d, J=6.3-6.8Hz), 1.37 and 1.43(9H, s), 2.20-2.70(1H, m), 2.55, 2.85 and 2.95, 3.05(6H, s), 3.15-3.40(2H, m), 3.65-3.85(2H, m), 4.75-5.20(2H, m), 5.40-5.50(1H, m), 6.40-6.65(1H, m), 6.75-6.85(1H, m), 6.95-7.15(1H, m), 7.25-7.35(2H, m), 7.58-7.63(2H, m)								

The synthesis scheme of Example 183 is shown in Scheme 18.

Scheme 18: Synthesis scheme of Example 183



The synthesis process of Scheme 18 is explained below:

10 Reaction step 1)

To a solution of Z-Trp-OH, N-Me-Val-N-Me-Tyr(3-tBu)-NH₂ and CMPI in THF, TEA was added under cooling and stirred at room temperature. The reaction mixture was mixed with water, extracted with ethyl acetate, washed with saturated brine, dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure; the thus obtained residue was purified by column chromatography (silica gel) to give Compound I-a183.

20

Reaction step 2)

To a solution of Compound I-a183 in methanol, Pd(OH)₂ was added and stirred in a hydrogen atmosphere at room temperature. After filtering off the Pd(OH)₂, the filtrate was concentrated under reduced pressure; the thus

obtained residue was purified by column chromatography
(silica gel) to give the titled compound.

Example conducted according to Scheme 18 is shown in
Table D-183.

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Table D-183

Example 183

Trp-N-Me-Val-N-Me-Tyr(3-tBu)-NH₂

Reaction1								
N-Me-Val-N-Me-Tyr(3-tBu)-NH ₂ (g)	Z-Trp-OH(g)	CMPI (g)	TEA (ml)	THF (ml)	Reaction time (hr)	Column sol.	Product	Amount (g)
0.620	0.700	0.660	0.48	15.00	24	MC:MeOH =30:1	I-a183	0.700
Reaction2								
Compound I-a183(g)	Pd(OH) ₂	MeOH (ml)	Reaction time (hr)	Column sol.	Amount (g)	HPLC min		
0.700	0.100	20.00	24	MC:MeOH =20:1	0.380	18.14		
ESI-MS(M ⁺ +1):550								
1H-NMR(CDCl ₃): (two rotamers) δ 0.39, 0.73 and 0.79, 0.93(6H, d, J=6.3-6.7Hz), 1.33 and 1.39(9H, s), 2.15-2.35(2H, m), 2.37, 2.75 and 2.95, 3.05(6H, s), 2.60-3.15(2H, m), 3.25-3.40(2H, m), 3.80-4.05(1H, m), 4.70-5.10(1H, m), 6.30-6.55(1H, m), 6.65-7.20(5H, m), 7.40-7.60(2H, m)								

Test Example 1

Motilin receptor binding test

09690219-121201
A motilin receptor binding test was conducted in the following manner [Vantrappen et al., Regul. Peptides, 15, 143 (1986)]. The duodenum was extracted from a slaughtered rabbit, had the mucous membrane separated and homogenized in 50 mM Tris buffer to prepare a protein sample. The protein sample was incubated together with ¹²⁵I motilin 25 pM and thereafter the radioactivity bound to the protein was measured. Specific binding was defined as the difference between the radioactivity in the case of adding a great excess amount of motilin (10^{-7} M) and that in the case of no adding. The activity of the compound was expressed by IC₅₀ (in nM), as the concentration sufficient to reduce the specific binding by 50%. Result is shown in Tables F-1 to F-3.

Test Example 2

Action on the contraction of a specimen of longitudinal muscle in the duodenum extracted from a rabbit

The action on the motilin-induced contraction of a specimen of longitudinal muscle in the duodenum extracted from a rabbit was investigated by the following method. A duodenum specimen (5 x 15 mm) extracted from a slaughtered rabbit was suspended in an organ bath (10 ml) such that the longitudinal muscle would run vertically; the bath was filled with a Krebs solution kept at 28°C. A mixed gas (95% O₂ and 5% CO₂) was continuously bubbled into the Krebs

solution and the contraction of the duodenum specimen was recorded isototonically (with a 1-g load) via an isotonic transducer (ME-3407, ME Commercial, Tokyo, Japan). The degree of contraction was expressed in relative values, 5 with the contraction by acetylcholine at a dose of 10^{-4} M being taken as 100%. The activity of the compound was calculated as pA_2 value indicating its effect on the dose-dependent muscle contraction by the motilin put into the organ bath. The result is shown in Tables F-1 to F-3.

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09890219-121201

Table F-1

Example No.	Motilin receptor binding test, IC_{50} (nM)	Contraction suppressing test, pA_2
1	0.89	8.8
2	0.71	8.7
3	1.5	8.7
4	1.6	8.3
8	0.35	9.5
9	1.0	9.0
12	0.52	9.3
14	0.70	9.3
15	0.82	8.5
16	0.41	9.4
17	0.70	9.1
19	2.2	8.7
21	0.27	9.8
22	0.52	8.3
23	0.67	9.3
24	0.94	9.1

Table F-2

Example No.	Motilin receptor binding test, IC ₅₀ (nM)	Contraction suppressing test, pA ₂
26	7.3	8.0
27	1.2	8.6
28	0.52	9.0
29	0.45	8.7
30	0.81	9.1
31	0.79	9.5
32	0.76	9.1
33	1.7	8.4
34	1.5	9.4
35	1.7	8.8
36	2.3	8.8
37	0.60	8.8
38	3.0	8.2
39	2.0	8.7
40	1.6	8.6
41	3.1	8.4
42	1.2	8.3
43	1.9	8.5
44	3.6	8.5
63	0.62	8.4
64	1.0	9.0
101	0.24	8.9
102	0.31	9.0
103	0.86	8.9

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Table F-3

Example No.	Motilin receptor binding test, IC_{50} (nM)	Contraction suppressing test, pA_2
104	0.32	9.1
105	0.31	9.8
106	0.62	9.8
107	0.39	8.7
108	0.43	9.0
109	0.17	8.7
119	0.40	9.4
120	0.27	9.0
121	0.41	8.9
122	0.47	9.0
123	0.70	9.1
124	0.98	9.1
125	1.0	9.0
126	1.9	9.2
127	1.7	8.7
128	1.5	8.7
129	4.0	8.5
132	0.86	8.9

FOI b7E b7C b7D b7F b7G b7H b7I b7J b7K b7L b7M b7N b7O b7P b7Q b7R b7S b7T b7U b7V b7W b7X b7Y b7Z

Table F-4

Example No.	Motilin receptor binding test, IC ₅₀ (nM)	Contraction suppressing test, pA ₂
133	1.1	8.2
134	1.5	8.3
135	0.70	8.5
136	6.8	7.6
140	4.0	8.2
142	0.62	8.6
144	2.0	8.5
148	4.1	8.4
151	0.36	8.2
155	2.5	8.1
157	6.1	8.1
163	2.4	7.8
165	2.8	8.2
166	1.8	9.8
182	2.3	8.5
183	0.57	9.5

INDUSTRIAL APPLICABILITY

- 5 The compounds of the present invention function as a motilin receptor antagonist and are useful as medicines including therapeutics of irritable bowel syndrome.